



Clinical trial results:

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and tolerability of RWJ333369 as adjunctive therapy in subjects with partial onset seizure

Summary

EudraCT number	2006-003941-17
Trial protocol	HU DK
Global end of trial date	12 October 2007

Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	333369EPY3002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00433667
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Antwerpseweg 15-17, B-2340 Beerse, Belgium,
Public contact	Clinical Registry Group, Janssen Research & Development, +353 21 4673500, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, +353 21 4673500, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000360-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 October 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 October 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Percent reduction in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor and/or complex partial, and/or secondarily generalized seizures during the double-blind treatment phase, relative to the pretreatment phase

Protection of trial subjects:

Safety was evaluated by monitoring of the frequency, severity, and timing of AEs, and by clinical laboratory test results, 12-lead electrocardiogram (ECG) recordings, vital signs measurements, physical and neurologic examinations, and pregnancy tests for females of child-bearing potential. In addition to safety monitoring by the Sponsor, a Data Safety Monitoring Board (DSMB) consisting of independent experts in the fields of epilepsy and biostatistics met to evaluate unblinded safety data from the study at pre-specified intervals in accordance with the DSMB charter.

Background therapy:

All subjects were receiving from 1-3 other antiepileptic drugs

Evidence for comparator:

Not a comparator study

Actual start date of recruitment	25 September 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	China: 74
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	India: 78
Country: Number of subjects enrolled	Norway: 13
Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Taiwan: 51
Country: Number of subjects enrolled	Thailand: 40
Country: Number of subjects enrolled	Ukraine: 95
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	562
EEA total number of subjects	143

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)	21
Adults (18-64 years)	531
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 721 subjects met the study entry criteria and were enrolled in the 8 week prospective baseline period from 12 countries.

Pre-assignment

Screening details:

In pre-treatment phase (Day -56 to -1) subjects continued with their Antiepileptic Drug (AED). Subject who met the following criteria: 1) at least 6 simple partial motor, complex partial, or secondarily generalized seizures per 56 days and no seizure-free interval for more than 3 weeks randomly assigned to double-blind treatment.

Period 1

Period 1 title	Double-blind Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.

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

Dosage and administration details:

Placebo matching with Carisbamate orally twice daily from Day 1 up to Week 12

Arm title	Carisbamate 200 mg
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Arm description:

The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.

Arm type	Experimental
Investigational medicinal product name	Carisbamate 200 milligram (mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

Arm title	Carisbamate 400 mg
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Arm description:

Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

Arm type	Active comparator
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Investigational medicinal product name	Carisbamate 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subject received Carisbamate 400 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

Number of subjects in period 1	Placebo	Carisbamate 200 mg	Carisbamate 400 mg
Started	189	188	185
Completed	178	176	174
Not completed	11	12	11
Consent withdrawn by subject	5	5	4
Adverse event, non-fatal	1	4	6
Other	-	2	-
Lost to follow-up	4	-	-
Protocol deviation	1	1	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.	
Reporting group title	Carisbamate 200 mg
Reporting group description:	
The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.	
Reporting group title	Carisbamate 400 mg
Reporting group description:	
Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.	

Reporting group values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg
Number of subjects	189	188	185
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	5	3	13
Adults (18-64 years)	181	183	167
From 65 to 84 years	3	2	5
85 years and over	0	0	0
Title for AgeContinuous Units: Years			
arithmetic mean	36	36.3	35.3
standard deviation	± 12.25	± 11.69	± 13.82
Title for Gender Units: subjects			
Female	110	92	88
Male	79	96	97

Reporting group values	Total		
Number of subjects	562		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	21		
Adults (18-64 years)	531		
From 65 to 84 years	10		
85 years and over	0		
Title for AgeContinuous Units: Years			
arithmetic mean			
standard deviation	-		
Title for Gender Units: subjects			
Female	290		
Male	272		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.	
Reporting group title	Carisbamate 200 mg
Reporting group description: The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.	
Reporting group title	Carisbamate 400 mg
Reporting group description: Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.	
Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intent-to-treat (ITT) population included all randomized subjects who had completed the seizure diary during both the baseline period and the double-blind phase.	

Primary: Percentage of Subjects who were Responders

End point title	Percentage of Subjects who were Responders
End point description: Responders are defined as subjects with $\geq 50\%$ reduction in partial onset seizures (POS) frequency during the double-blind treatment phase, relative to the pretreatment baseline phase.	
End point type	Primary
End point timeframe: Day 85	

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	188 ^[1]	186 ^[2]	181 ^[3]	
Units: Percentage of Subjects				
number (not applicable)	21.3	23.1	23.8	

Notes:

[1] - ITT Population

[2] - ITT Population

[3] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v Carisbamate 200 mg

Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.637 ^[4]
Method	Generalized Cochran-Mantel-Haenszel test
Parameter estimate	Difference between treatment groups
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.58
upper limit	10.26

Notes:

[4] - Pairwise comparison: p-values from Generalized Cochran-Mantel-Haenszel test for nonzero correlation controlling for pooled country.

Statistical analysis title	Statistical analysis
Comparison groups	Carisbamate 400 mg v Placebo
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.553 ^[5]
Method	Generalized Cochran-Mantel-Haenszel tes
Parameter estimate	Difference between treatment groups
Point estimate	2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.04
upper limit	11

Notes:

[5] - p-values from Generalized Cochran-Mantel-Haenszel test for nonzero correlation controlling for pooled country.

Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in the Recovery (After Seizures) Composite Score of the Seizure Severity Questionnaire (SSQ) Score

End point title	Change From Baseline to the end of the Double-Blind Treatment Phase in the Recovery (After Seizures) Composite Score of the Seizure Severity Questionnaire (SSQ) Score
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End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity. It is organized into 3 components: the Warning, Activity-movement, and Recovery aspects of seizures. The score of SSQ ranges on a 7-point Likert scale (ranging from very mild/helpful/no bother at all [1] to very severe/no help/bothersome [7]) and lower scores represent better function. Recovery Phase Composite Score were reported.

End point type	Secondary
End point timeframe:	
Baseline up to Day 85	

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	188 ^[6]	185 ^[7]	180 ^[8]	
Units: Unit on a Scale				
arithmetic mean (standard deviation)	-0.6 (± 1.91)	-0.8 (± 2.02)	-1 (± 2.01)	

Notes:

[6] - ITT Population

[7] - ITT Population

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Seizure Severity Questionnaire (SSQ) Score

End point title	Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Seizure Severity Questionnaire (SSQ) Score
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End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity. It is organized into 3 components: the Warning, Activity-movement, and Recovery aspects of seizures. The score of SSQ ranges on a 7-point Likert scale (ranging from very mild/helpful/no bother at all [1] to very severe/no help/bothersome [7]) and lower scores represent better function.

End point type	Secondary
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End point timeframe:

Baseline up to Day 85 (Endpoint)

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173 ^[9]	171 ^[10]	168 ^[11]	
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Total SSQ score	3.9 (± 1.3)	3.8 (± 1.22)	3.9 (± 1.31)	
Change at Endpoint (EP): Total SSQ score	-0.8 (± 1.58)	-0.9 (± 1.66)	-0.9 (± 1.59)	
BL: Before seizures component score	3.6 (± 2.14)	3.6 (± 1.97)	3.8 (± 1.77)	
Change at EP: Before seizures component score	-0.4 (± 2.36)	-0.5 (± 2.43)	-0.6 (± 2.01)	
BL: During seizures component score	4.3 (± 1.5)	4.3 (± 1.5)	4.3 (± 1.58)	
Change at EP: During seizures component score	-0.8 (± 1.78)	-0.9 (± 1.99)	-0.8 (± 2.06)	
BL: Severity and bother component score	4.4 (± 1.48)	4.4 (± 1.25)	4.4 (± 1.37)	
Change at EP: Severity and bother component score	-0.9 (± 1.82)	-1.1 (± 1.84)	-0.9 (± 1.9)	
BL: cognitive subcomponent score	2.8 (± 2.64)	2.9 (± 2.54)	2.8 (± 2.6)	
Change at EP: cognitive subcomponent score	-0.6 (± 2.45)	-0.9 (± 2.38)	-1.1 (± 2.45)	
BL: emotional subcomponent score	2.2 (± 2.52)	2.3 (± 2.54)	2.2 (± 2.53)	
Change at EP: emotional subcomponent score	-0.5 (± 2.41)	-0.8 (± 2.2)	-0.8 (± 2.57)	

BL: physical effects subcomponent score	3.4 (± 2.55)	3.1 (± 2.53)	3.5 (± 2.52)	
Change at EP: physical effects subcomponent score	-0.8 (± 2.34)	-0.9 (± 2.63)	-1.2 (± 2.46)	
BL: frequency subcomponent score	3.1 (± 2.3)	3 (± 2.36)	3.1 (± 2.33)	
Change at EP: frequency subcomponent score	-0.7 (± 2.13)	-0.8 (± 2.2)	-1.1 (± 2.15)	
BL: severity subcomponent score	2.6 (± 2.03)	2.6 (± 2.11)	2.6 (± 2.03)	
Change at EP: severity subcomponent score	-0.6 (± 1.82)	-0.8 (± 1.96)	-1 (± 1.95)	
BL: bother subcomponent score	2.7 (± 2.14)	2.7 (± 2.24)	2.7 (± 2.23)	
Change at EP: bother subcomponent score	-0.6 (± 2)	-0.9 (± 2.13)	-1 (± 2.17)	

Notes:

[9] - ITT Population

[10] - ITT Population

[11] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Quality of Life in Epilepsy-31-Problems (QOLIE-31-P) Score

End point title	Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Quality of Life in Epilepsy-31-Problems (QOLIE-31-P) Score
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End point description:

The QOLIE-31-P is an expansion of the QOLIE-31 which includes items to assess distress associated with each quality of life domain, overall change in distress, and priority of importance of each domain. It is a 39-item self-administered questionnaire designed to assess generic and epilepsy specific health-related issues. It includes 7 subscales: seizure worry, overall quality of life (QOL), emotional well-being, energy-fatigue, cognitive functioning, medication effects, social function, the health status item, and the additional items on distress and priority of importance of each of the domains. Higher scores represent better function.

End point type	Secondary
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End point timeframe:

Baseline up Day 85 (Endpoint)

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174 ^[12]	169 ^[13]	169 ^[14]	
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Overall Score	57 (± 14.96)	55.7 (± 16.32)	55.3 (± 16.47)	
Change at Endpoint (EP): Overall Score	4.3 (± 10.75)	3.6 (± 10.53)	4.5 (± 10.85)	
BL: Seizure worry	43.6 (± 27.81)	43 (± 25.39)	43.3 (± 27.47)	
Change at EP: Seizure worry	7.2 (± 21.03)	6.4 (± 19.89)	6 (± 22.34)	
BL: Overall quality of life	58.2 (± 15.56)	56.8 (± 16)	54.8 (± 16.85)	
Change at EP: Overall quality of life	5.6 (± 15.63)	5.2 (± 15.05)	5.1 (± 14.36)	
BL: Emotional well-being	62.6 (± 18.07)	61.3 (± 18.29)	60.7 (± 19.17)	
Change at EP: Emotional well-being	3.6 (± 14.63)	2.2 (± 14.25)	4.1 (± 16.03)	

BL: Energy-fatigue	54 (± 16.07)	55.3 (± 18.18)	55.6 (± 19.38)	
Change at EP: Energy-fatigue	4.3 (± 14.96)	3.2 (± 16.34)	3.9 (± 16.66)	
BL: Cognitive function	57.6 (± 23.41)	55.7 (± 24.37)	56.2 (± 22.34)	
Change at EP: Cognitive function	4.1 (± 16.93)	2.4 (± 16.81)	4.2 (± 17.19)	
BL: Medication effects	59.6 (± 27.11)	56.8 (± 28.27)	59.1 (± 25.27)	
Change at EP: Medication effects	-0.8 (± 27.32)	5.3 (± 23.51)	1.6 (± 22.34)	
BL: Social function	57.8 (± 22.3)	55.8 (± 23.45)	54.7 (± 24.98)	
Change at EP: Social function	4 (± 21.02)	4.2 (± 20.41)	5.1 (± 21.79)	
BL: Visual analog health status	60.2 (± 17.32)	59.2 (± 18.39)	55.3 (± 19.7)	
Change at EP: Visual analog health status	3.7 (± 19.75)	5.1 (± 17.29)	6.1 (± 18.74)	

Notes:

[12] - ITT population

[13] - ITT Population

[14] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in Hospital Anxiety and Depression Scale (HADS) Score

End point title	Change From Baseline to the end of the Double-Blind Treatment Phase in Hospital Anxiety and Depression Scale (HADS) Score
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End point description:

The HADS is a brief, self-administered questionnaire designed to assess the presence of an anxiety or depressive disorder in medically ill outpatients in non-psychiatric hospital settings. The HADS consists of Anxiety and Depression subscales. Each item is rated on a 4-point scale from 0 to 3 representing frequency of symptoms. For each subscale, higher scores indicate greater dysfunction.

End point type	Secondary
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End point timeframe:

Baseline up to Day 85 (Endpoint)

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174 ^[15]	168 ^[16]	169 ^[17]	
Units: Unit on a Scale				
arithmetic mean (standard deviation)				
Baseline: Depression score	6 (± 3.97)	5.7 (± 3.7)	5.9 (± 3.88)	
Change at Endpoint: Depression score	-0.9 (± 3.74)	-0.9 (± 3.18)	-0.8 (± 3.09)	
Baseline: Anxiety score	7.4 (± 3.87)	7.9 (± 3.8)	7.5 (± 3.72)	
Change at Endpoint: Anxiety score	-0.8 (± 3.4)	-1 (± 2.91)	-1.2 (± 3.18)	

Notes:

[15] - ITT Population

[16] - ITT Population

[17] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in EuroQol-5D (EQ-5D) Score

End point title	Change From Baseline to the end of the Double-Blind Treatment Phase in EuroQol-5D (EQ-5D) Score
End point description: The EQ-5D is a 5-dimensional health state classification to assess preference-based health-related functional status. The 5 dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated by a single question on a 3-point ordinal scale (no problems, some problems, extreme problems). Higher scores on this self-administered scale represent better health.	
End point type	Secondary
End point timeframe: Baseline up to Day 85 (Endpoint)	

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174 ^[18]	167 ^[19]	169 ^[20]	
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Baseline: Overall utility score	0.75 (± 0.232)	0.78 (± 0.214)	0.76 (± 0.224)	
Change at Endpoint: Overall utility score	0.04 (± 0.241)	0.03 (± 0.233)	0.08 (± 0.209)	
Baseline: Self-reported VAS score	65.89 (± 17.549)	66.07 (± 18.771)	63.83 (± 21.705)	
Change at Endpoint: Self-reported VAS score	2.18 (± 18.272)	3.31 (± 16.013)	4.09 (± 18.697)	

Notes:

[18] - ITT Population

[19] - ITT Population

[20] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Reduction From Baseline to Double Blind Treatment in Generalized Seizures

End point title	Percent Reduction From Baseline to Double Blind Treatment in Generalized Seizures
End point description: Change in generalized seizure frequency evaluated as the percent reduction from the pretreatment baseline phase in generalized seizure frequency compared with the double blind treatment phase	
End point type	Secondary
End point timeframe: Baseline up to Day 85 (Endpoint)	

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84 ^[21]	95 ^[22]	81 ^[23]	
Units: Percent Change				
median (full range (min-max))				
Baseline	3.1 (0 to 34)	2.4 (0 to 72)	2.5 (0 to 62)	
Percent Change at Endpoint	28.3 (-340 to 100)	35.9 (-340 to 100)	29.3 (-340 to 100)	

Notes:

[21] - ITT Population

[22] - ITT Population

[23] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Reduction from Baseline to Double Blind Treatment in Average Monthly Seizure-Free Days

End point title	Percent Reduction from Baseline to Double Blind Treatment in Average Monthly Seizure-Free Days
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End point description:

Seizure-free days evaluated as the percent change from the pretreatment baseline phase in average monthly seizure-free days per 28 days compared with the double-blind treatment phase.

End point type	Secondary
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End point timeframe:

Baseline up to Day 85 (Endpoint)

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	188 ^[24]	186 ^[25]	181 ^[26]	
Units: Percent Chanes				
arithmetic mean (standard deviation)				
Baseline	20 (± 6.18)	20 (± 5.81)	20.2 (± 5.28)	
Percent Change at Endpoint	15.9 (± 75.86)	33.6 (± 265.6)	17.6 (± 102.32)	

Notes:

[24] - ITT Population

[25] - ITT Population

[26] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Reduction from Baseline to Double Blind Treatment in Partial Onset Seizure Frequency

End point title	Percent Reduction from Baseline to Double Blind Treatment in Partial Onset Seizure Frequency
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End point description:

Change in Partial Onset Seizure Frequency evaluated as the percent reduction from the pretreatment baseline phase in Partial Onset Seizure Frequency compared with the double blind treatment phase

End point type	Secondary
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End point timeframe:

Baseline up to Day 85 (Endpoint)

End point values	Placebo	Carisbamate 200 mg	Carisbamate 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	188 ^[27]	186 ^[28]	181 ^[29]	
Units: Percent change				
median (full range (min-max))				
Baseline	6.75 (2.5 to 260.4)	7 (2 to 274.2)	7.5 (2 to 258.2)	
Percentage Change at Endpoint	15.11 (-308 to 100)	21.59 (-280 to 100)	21.03 (-692 to 100)	

Notes:

[27] - ITT Population

[28] - ITT Population

[29] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to End of treatment

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.

Reporting group title	Carisbamate 400 mg
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Reporting group description:

Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

Reporting group title	Carisbamate 200 mg
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Reporting group description:

The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.

Serious adverse events	Placebo	Carisbamate 400 mg	Carisbamate 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 189 (2.65%)	5 / 185 (2.70%)	4 / 188 (2.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Electrocardiogram T Wave Inversion			
subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm Progression			
subjects affected / exposed	0 / 189 (0.00%)	1 / 185 (0.54%)	0 / 188 (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
Injury, poisoning and procedural complications			
Ankle Fracture			

subjects affected / exposed	1 / 189 (0.53%)	0 / 185 (0.00%)	0 / 188 (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
Contusion			
subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Vertebral Fracture			
subjects affected / exposed	1 / 189 (0.53%)	0 / 185 (0.00%)	0 / 188 (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 / 189 (0.53%)	0 / 185 (0.00%)	0 / 188 (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			
Epilepsy			
subjects affected / exposed	1 / 189 (0.53%)	0 / 185 (0.00%)	0 / 188 (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 / 189 (0.00%)	1 / 185 (0.54%)	0 / 188 (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
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	1 / 188 (0.53%)
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			

Gastritis			
subjects affected / exposed	0 / 189 (0.00%)	1 / 185 (0.54%)	0 / 188 (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
Haematochezia			
subjects affected / exposed	1 / 189 (0.53%)	0 / 185 (0.00%)	0 / 188 (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
Vomiting			
subjects affected / exposed	0 / 189 (0.00%)	1 / 185 (0.54%)	0 / 188 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 185 (0.00%)	0 / 188 (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			
subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Furuncle			
subjects affected / exposed	0 / 189 (0.00%)	1 / 185 (0.54%)	0 / 188 (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
Hepatitis B			
subjects affected / exposed	0 / 189 (0.00%)	1 / 185 (0.54%)	0 / 188 (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
Viral Infection			
subjects affected / exposed	0 / 189 (0.00%)	1 / 185 (0.54%)	0 / 188 (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: 1 %

Non-serious adverse events	Placebo	Carisbamate 400 mg	Carisbamate 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 189 (44.97%)	96 / 185 (51.89%)	86 / 188 (45.74%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 189 (1.59%)	1 / 185 (0.54%)	0 / 188 (0.00%)
occurrences (all)	11	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 189 (0.53%)	3 / 185 (1.62%)	3 / 188 (1.60%)
occurrences (all)	1	3	3
Chest Pain			
subjects affected / exposed	1 / 189 (0.53%)	1 / 185 (0.54%)	2 / 188 (1.06%)
occurrences (all)	1	1	3
Fatigue			
subjects affected / exposed	3 / 189 (1.59%)	7 / 185 (3.78%)	4 / 188 (2.13%)
occurrences (all)	4	7	5
Irritability			
subjects affected / exposed	1 / 189 (0.53%)	0 / 185 (0.00%)	3 / 188 (1.60%)
occurrences (all)	1	0	3
Oedema Peripheral			
subjects affected / exposed	2 / 189 (1.06%)	0 / 185 (0.00%)	2 / 188 (1.06%)
occurrences (all)	2	0	3
Pyrexia			
subjects affected / exposed	2 / 189 (1.06%)	4 / 185 (2.16%)	6 / 188 (3.19%)
occurrences (all)	2	4	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 189 (0.53%)	0 / 185 (0.00%)	2 / 188 (1.06%)
occurrences (all)	2	0	2

Pharyngolaryngeal Pain subjects affected / exposed occurrences (all)	3 / 189 (1.59%) 3	1 / 185 (0.54%) 1	1 / 188 (0.53%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	2 / 189 (1.06%) 2	1 / 185 (0.54%) 2	2 / 188 (1.06%) 2
Insomnia subjects affected / exposed occurrences (all)	3 / 189 (1.59%) 3	5 / 185 (2.70%) 10	1 / 188 (0.53%) 1
Investigations			
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	3 / 189 (1.59%) 3	3 / 185 (1.62%) 3	2 / 188 (1.06%) 2
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	3 / 189 (1.59%) 3	3 / 185 (1.62%) 3	2 / 188 (1.06%) 2
Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	2 / 189 (1.06%) 2	0 / 185 (0.00%) 0	3 / 188 (1.60%) 3
Blood Creatine Phosphokinase Increased subjects affected / exposed occurrences (all)	1 / 189 (0.53%) 1	1 / 185 (0.54%) 1	3 / 188 (1.60%) 4
Blood Glucose Increased subjects affected / exposed occurrences (all)	0 / 189 (0.00%) 0	1 / 185 (0.54%) 1	2 / 188 (1.06%) 2
International Normalised Ratio Increased subjects affected / exposed occurrences (all)	1 / 189 (0.53%) 1	2 / 185 (1.08%) 2	0 / 188 (0.00%) 0
Neutrophil Count Decreased subjects affected / exposed occurrences (all)	1 / 189 (0.53%) 1	0 / 185 (0.00%) 0	3 / 188 (1.60%) 4
Platelet Count Decreased			

subjects affected / exposed occurrences (all)	2 / 189 (1.06%) 2	1 / 185 (0.54%) 2	2 / 188 (1.06%) 2
Red Blood Cell Count Decreased subjects affected / exposed occurrences (all)	0 / 189 (0.00%) 0	0 / 185 (0.00%) 0	2 / 188 (1.06%) 2
Weight Increased subjects affected / exposed occurrences (all)	3 / 189 (1.59%) 3	0 / 185 (0.00%) 0	1 / 188 (0.53%) 1
White Blood Cell Count Decreased subjects affected / exposed occurrences (all)	3 / 189 (1.59%) 3	1 / 185 (0.54%) 1	2 / 188 (1.06%) 2
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 189 (0.53%) 1	2 / 185 (1.08%) 2	0 / 188 (0.00%) 0
Excoriation subjects affected / exposed occurrences (all)	0 / 189 (0.00%) 0	0 / 185 (0.00%) 0	3 / 188 (1.60%) 4
Skin Laceration subjects affected / exposed occurrences (all)	2 / 189 (1.06%) 2	1 / 185 (0.54%) 1	1 / 188 (0.53%) 1
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	2 / 189 (1.06%) 2	1 / 185 (0.54%) 1	0 / 188 (0.00%) 0
Sinus Bradycardia subjects affected / exposed occurrences (all)	0 / 189 (0.00%) 0	3 / 185 (1.62%) 3	1 / 188 (0.53%) 1
Nervous system disorders			
Amnesia subjects affected / exposed occurrences (all)	1 / 189 (0.53%) 1	2 / 185 (1.08%) 2	0 / 188 (0.00%) 0
Balance Disorder subjects affected / exposed occurrences (all)	1 / 189 (0.53%) 1	0 / 185 (0.00%) 0	4 / 188 (2.13%) 5
Coordination Abnormal			

subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	2 / 188 (1.06%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	13 / 189 (6.88%)	24 / 185 (12.97%)	16 / 188 (8.51%)
occurrences (all)	16	30	23
Epilepsy			
subjects affected / exposed	1 / 189 (0.53%)	4 / 185 (2.16%)	2 / 188 (1.06%)
occurrences (all)	1	4	3
Headache			
subjects affected / exposed	22 / 189 (11.64%)	22 / 185 (11.89%)	24 / 188 (12.77%)
occurrences (all)	80	51	82
Hypokinesia			
subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	2 / 188 (1.06%)
occurrences (all)	0	0	2
Memory Impairment			
subjects affected / exposed	2 / 189 (1.06%)	0 / 185 (0.00%)	1 / 188 (0.53%)
occurrences (all)	2	0	1
Paraesthesia			
subjects affected / exposed	0 / 189 (0.00%)	1 / 185 (0.54%)	2 / 188 (1.06%)
occurrences (all)	0	1	3
Somnolence			
subjects affected / exposed	7 / 189 (3.70%)	17 / 185 (9.19%)	17 / 188 (9.04%)
occurrences (all)	9	17	26
Speech Disorder			
subjects affected / exposed	0 / 189 (0.00%)	0 / 185 (0.00%)	2 / 188 (1.06%)
occurrences (all)	0	0	2
Tremor			
subjects affected / exposed	1 / 189 (0.53%)	1 / 185 (0.54%)	3 / 188 (1.60%)
occurrences (all)	1	1	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 189 (1.06%)	1 / 185 (0.54%)	0 / 188 (0.00%)
occurrences (all)	2	1	0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed occurrences (all)	3 / 189 (1.59%) 5	4 / 185 (2.16%) 4	4 / 188 (2.13%) 4
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 189 (0.00%)	3 / 185 (1.62%)	1 / 188 (0.53%)
occurrences (all)	0	6	1
Lacrimation Increased			
subjects affected / exposed	0 / 189 (0.00%)	2 / 185 (1.08%)	1 / 188 (0.53%)
occurrences (all)	0	2	1
Vision Blurred			
subjects affected / exposed	2 / 189 (1.06%)	2 / 185 (1.08%)	4 / 188 (2.13%)
occurrences (all)	2	3	4
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	3 / 189 (1.59%)	1 / 185 (0.54%)	0 / 188 (0.00%)
occurrences (all)	4	14	0
Abdominal Pain Upper			
subjects affected / exposed	7 / 189 (3.70%)	2 / 185 (1.08%)	4 / 188 (2.13%)
occurrences (all)	8	2	5
Constipation			
subjects affected / exposed	2 / 189 (1.06%)	3 / 185 (1.62%)	2 / 188 (1.06%)
occurrences (all)	2	3	3
Diarrhoea			
subjects affected / exposed	2 / 189 (1.06%)	6 / 185 (3.24%)	3 / 188 (1.60%)
occurrences (all)	2	7	3
Nausea			
subjects affected / exposed	5 / 189 (2.65%)	5 / 185 (2.70%)	5 / 188 (2.66%)
occurrences (all)	5	5	5
Toothache			
subjects affected / exposed	2 / 189 (1.06%)	1 / 185 (0.54%)	0 / 188 (0.00%)
occurrences (all)	2	1	0
Vomiting			
subjects affected / exposed	1 / 189 (0.53%)	3 / 185 (1.62%)	3 / 188 (1.60%)
occurrences (all)	1	4	6
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	6 / 189 (3.17%)	0 / 185 (0.00%)	0 / 188 (0.00%)
occurrences (all)	6	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 189 (0.00%)	2 / 185 (1.08%)	0 / 188 (0.00%)
occurrences (all)	0	2	0
Pruritus			
subjects affected / exposed	0 / 189 (0.00%)	2 / 185 (1.08%)	2 / 188 (1.06%)
occurrences (all)	0	2	2
Pruritus Generalised			
subjects affected / exposed	2 / 189 (1.06%)	0 / 185 (0.00%)	0 / 188 (0.00%)
occurrences (all)	3	0	0
Rash			
subjects affected / exposed	0 / 189 (0.00%)	3 / 185 (1.62%)	4 / 188 (2.13%)
occurrences (all)	0	3	4
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 189 (1.59%)	3 / 185 (1.62%)	3 / 188 (1.60%)
occurrences (all)	3	3	3
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 189 (1.06%)	0 / 185 (0.00%)	1 / 188 (0.53%)
occurrences (all)	2	0	1
Musculoskeletal Pain			
subjects affected / exposed	2 / 189 (1.06%)	0 / 185 (0.00%)	2 / 188 (1.06%)
occurrences (all)	2	0	2
Myalgia			
subjects affected / exposed	1 / 189 (0.53%)	1 / 185 (0.54%)	2 / 188 (1.06%)
occurrences (all)	1	1	2
Pain in Extremity			
subjects affected / exposed	1 / 189 (0.53%)	2 / 185 (1.08%)	3 / 188 (1.60%)
occurrences (all)	2	2	3
Infections and infestations			
Gastroenteritis Viral			
subjects affected / exposed	0 / 189 (0.00%)	2 / 185 (1.08%)	0 / 188 (0.00%)
occurrences (all)	0	2	0
Influenza			

subjects affected / exposed occurrences (all)	2 / 189 (1.06%) 2	1 / 185 (0.54%) 1	2 / 188 (1.06%) 4
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 189 (3.70%) 9	5 / 185 (2.70%) 6	7 / 188 (3.72%) 8
Pharyngitis subjects affected / exposed occurrences (all)	2 / 189 (1.06%) 2	0 / 185 (0.00%) 0	0 / 188 (0.00%) 0
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	7 / 189 (3.70%) 10	6 / 185 (3.24%) 8	13 / 188 (6.91%) 16
Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 189 (0.53%) 1	3 / 185 (1.62%) 3	2 / 188 (1.06%) 2
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	0 / 189 (0.00%) 0	1 / 185 (0.54%) 1	2 / 188 (1.06%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2007	Clarifications were made to inclusion and exclusion criteria to assist investigators with determination of subject eligibility. In addition, subjects with congenital short QT syndrome were now excluded. For the efficacy analyses, the statistical method for the step-down procedure performed as the primary analysis for the United States was revised to exclude the responder rate as an endpoint to be analyzed sequentially. Adjustment in the total blood volume drawn as a result of the addition of coagulation tests to the final double-blind visit, deletion of a serum lipid profile at Visit 1, addition of a subject education video, instructions for the calculation of seizure frequency during the baseline period, more detailed procedures on drug accountability monitoring, a change to study drug packaging, and a change to the visit window for the final follow-up visit from 7 to 14 days after the last dose of study drug to 7 days after the last dose of study drug.
11 September 2007	The study objectives, hypotheses, statistical methods, and efficacy analyses were revised to present the primary and secondary efficacy end points by group for registration in the United States and ROW and in the countries of Europe, Australia, New Zealand, and South Africa, to meet United States and EMEA requirements. The responder rate was moved from a secondary end point in the United States and ROW to a primary end point for registration in Europe, Australia, New Zealand, and South Africa to meet Committee for Human Medicinal Products (CHMP) guideline requirements. Additional cardiovascular assessment procedures were added to further establish cardiac risk factors, including the collection of smoking history and family history of coronary artery disease and sudden death at the screening visit, evaluation and measurement of the QTc interval using Fridericia's correction (QTcF), and additional cardiac-related outcomes of interest to the safety analyses. Clinically insignificant and minor variance in the hemoglobin test values at screening for menstruating women in the exclusion criterion was made acceptable, if women were asymptomatic. Analysis of additional SSQ domains was added, and clarifications were made to the statistical analyses methods for secondary efficacy end points. Clarifications to the safety analyses for vital signs, physical and neurologic examinations, and Physician Withdrawal Checklist scores were also made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported