Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of RWJ-333369 as Adjunctive Therapy in Subjects with Partial Onset Seizures Followed by an Open-Label Extension Study

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2006-003839-68
Trial protocol	FI SE DE CZ
Global end of trial date	05 October 2010

Results information

Result version number	v2 (current)
This version publication date	02 June 2016
First version publication date	03 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	333369-EPY-3001/3004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00425282
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Turnhoutseweg 30, 2340 Beerse, Belgium,
Public contact	Janssen-Cilag International N.V., Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen-Cilag International N.V., Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the efficacy, safety, and tolerability of carisbamate (CRS) 200 and 400 milligram per day (mg/d) as adjunctive treatment of partial onset seizures (POS).

Protection of trial subjects:

Safety was monitored by means of Data Safety Monitoring Board (DSMB). Safety was evaluated by examining the incidence and severity of adverse events, evaluation of clinical laboratory tests (hematology, serum chemistry, serum lipid profile and urinalysis), vital signs, 12-lead electrocardiogram (ECGs), physical and neurological examination, and assessment of physician withdrawal checklist.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2007
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	Argentina: 39
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	China: 53
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Czech Republic: 48
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	India: 75
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Korea, Republic of: 64
Country: Number of subjects enrolled	Russian Federation: 105
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	United States: 85
Worldwide total number of subjects	565
EEA total number of subjects	114

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)	23
Adults (18-64 years)	532
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who successfully completed the 8-week prospective baseline period and experienced at least 6 simple partial motor, complex partial, or secondarily generalized seizures per 56 days, with no seizure-free period of more than 3 weeks during the baseline period, were allowed to enter into the double blind treatment phase.

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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo orally from Day 1 and remained on placebo for the next 12 weeks.

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

Dosage and administration details:

Subjects received placebo orally for 12 weeks.

Arm title	CRS 200 mg/day

Arm description:

Subjects received their randomly assigned dosage, CRS 200 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Carisbamate
Investigational medicinal product code	
Other name	(S)-2-O-carbamoyl-1-O-chlorophenyl-ethanol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received CRS 200 mg/day orally for 12 weeks.

Arm title	CRS 400 mg/day

Arm description:

Subjects received their randomly assigned dosage, CRS 400 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.

Arm type	Experimental

Investigational medicinal product name	Carisbamate
Investigational medicinal product code	
Other name	(S)-2-O-carbamoyl-1-O-chlorophenyl-ethanol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received CRS 400 mg/day orally for 12 weeks.

Number of subjects in period 1	Placebo	CRS 200 mg/day	CRS 400 mg/day
Started	186	187	192
Completed	171	176	180
Not completed	15	11	12
Consent withdrawn by subject	3	5	2
Adverse event, non-fatal	7	1	7
Other	2	1	-
Pregnancy	1	-	1
Adverse event, serious non-fatal	-	1	2
Lost to follow-up	-	1	-
Protocol deviation	2	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo orally from Day 1 and remained on placebo for the next 12 weeks.	
Reporting group title	CRS 200 mg/day
Reporting group description:	
Subjects received their randomly assigned dosage, CRS 200 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.	
Reporting group title	CRS 400 mg/day
Reporting group description:	
Subjects received their randomly assigned dosage, CRS 400 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.	

Reporting group values	Placebo	CRS 200 mg/day	CRS 400 mg/day
Number of subjects	186	187	192
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	7	6	10
Adults (18-64 years)	175	177	180
From 65 to 84 years	4	4	2
85 years and over	0	0	0
Title for AgeContinuous Units: Years			
arithmetic mean	36	35.1	34.8
standard deviation	± 13.06	± 12.11	± 12.89
Title for Gender Units: subjects			
Female	99	95	86
Male	87	92	106

Reporting group values	Total		
Number of subjects	565		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	23		
Adults (18-64 years)	532		
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	280		

Male	285		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo orally from Day 1 and remained on placebo for the next 12 weeks.	
Reporting group title	CRS 200 mg/day
Reporting group description:	
Subjects received their randomly assigned dosage, CRS 200 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.	
Reporting group title	CRS 400 mg/day
Reporting group description:	
Subjects received their randomly assigned dosage, CRS 400 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.	

Primary: Percent Reduction From Baseline to Double Blind Phase in Partial Onset Seizure Frequency

End point title	Percent Reduction From Baseline to Double Blind Phase in Partial Onset Seizure Frequency
End point 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.	
End point type	Primary
End point timeframe:	
Baseline up to Day 85	

End point values	Placebo	CRS 200 mg/day	CRS 400 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183[1]	187	191[2]	
Units: percent reduction				
median (full range (min-max))	15.21 (-1300 to 100)	16.44 (-190 to 100)	27.27 (-262 to 100)	

Notes:

[1] - Here 'N' signifies number of subjects analysed for this endpoint.

[2] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v CRS 200 mg/day
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.678
Method	Wilcoxon rank sum test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v CRS 400 mg/day
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Wilcoxon rank sum test

Secondary: Change from Baseline to the End of Double Blind Treatment Phase in the Seizure Severity Questionnaire (SSQ) Recovery Phase Composite Score (RPCS)

End point title	Change from Baseline to the End of Double Blind Treatment Phase in the Seizure Severity Questionnaire (SSQ) Recovery Phase Composite Score (RPCS)

End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity signs and is formatted as a structured interview. It is organized into 3 components: the Warning, Activity-movement, and Recovery (cognitive, emotional, and physical) aspects of seizures. Questions review duration, severity, bothersomeness, and overall ratings, and the most bothersome aspect of seizures. Lower scores represent better function. The ITT population included all randomized subjects who had completed the seizure diary during both the baseline period and the double-blind phase.

End point type	Secondary

End point timeframe:

Baseline up to Day 85

End point values	Placebo	CRS 200 mg/day	CRS 400 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	182[3]	185[4]	189[5]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 43 (n= 172, 177, 181)	-0.6 (± 1.73)	-0.5 (± 1.76)	-0.6 (± 1.81)	
Day 85 (n= 170, 173, 178)	-0.7 (± 1.86)	-0.6 (± 1.62)	-0.5 (± 1.81)	
Endpoint (n= 182, 184, 189)	-0.7 (± 1.83)	-0.5 (± 1.59)	-0.4 (± 1.84)	

Notes:

[3] - Here 'N' signifies number of subjects analysed for this endpoint.

[4] - Here 'N' signifies number of subjects analysed for this endpoint.

[5] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Double Blind End Point in SSQ Scores

End point title	Change From Baseline to Double Blind End Point in SSQ Scores

End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity signs and is formatted as a structured interview. It is organized into 3 components: the Warning, Activity-movement, and Recovery (cognitive, emotional, and physical) aspects of seizures. Questions review duration, severity, bothersomeness, and overall ratings, and the most bothersome aspect of seizures. Lower scores represent better function. 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.

End point type	Secondary

End point timeframe:

Baseline up to Day 85

End point values	Placebo	CRS 200 mg/day	CRS 400 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175[6]	174[7]	180[8]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	3.7 (± 1.26)	3.7 (± 1.21)	3.8 (± 1.26)	
End Point	-0.6 (± 1.5)	-0.6 (± 1.28)	-0.5 (± 1.38)	

Notes:

[6] - Here 'N' signifies number of subjects analysed for this endpoint.

[7] - Here 'N' signifies number of subjects analysed for this endpoint.

[8] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to End of study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0
Reporting groups	
Reporting group title	PLACEBO
Reporting group description: Placebo	
Reporting group title	CRS 400mg
Reporting group description: CARISBAMATE 400 mg per day	
Reporting group title	CRS 200mg
Reporting group description: CARISBAMATE 200 mg per day	

Serious adverse events	PLACEBO	CRS 400mg	CRS 200mg
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 186 (4.30%)	5 / 192 (2.60%)	10 / 187 (5.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (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
Facial Bones Fracture			
subjects affected / exposed	1 / 186 (0.54%)	0 / 192 (0.00%)	0 / 187 (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
Joint Dislocation			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (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
Lower Limb Fracture			

subjects affected / exposed	0 / 186 (0.00%)	1 / 192 (0.52%)	0 / 187 (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
Rib Fracture			
subjects affected / exposed	1 / 186 (0.54%)	0 / 192 (0.00%)	0 / 187 (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
Skin Injury			
subjects affected / exposed	0 / 186 (0.00%)	1 / 192 (0.52%)	0 / 187 (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
Skin Laceration			
subjects affected / exposed	1 / 186 (0.54%)	0 / 192 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Brain Injury			
subjects affected / exposed	1 / 186 (0.54%)	0 / 192 (0.00%)	0 / 187 (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	2 / 186 (1.08%)	1 / 192 (0.52%)	3 / 187 (1.60%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand Mal Convulsion			
subjects affected / exposed	2 / 186 (1.08%)	0 / 192 (0.00%)	0 / 187 (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
Status Epilepticus			
subjects affected / exposed	3 / 186 (1.61%)	1 / 192 (0.52%)	0 / 187 (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
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (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			
Abdominal Distension			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (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
Skin and subcutaneous tissue disorders			
Rash Generalised			
subjects affected / exposed	0 / 186 (0.00%)	1 / 192 (0.52%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic Disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 192 (0.52%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary Retention			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 186 (0.54%)	0 / 192 (0.00%)	0 / 187 (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
Pneumonia Necrotising			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (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
Urinary Tract Infection			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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	CRS 400mg	CRS 200mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 186 (43.55%)	101 / 192 (52.60%)	81 / 187 (43.32%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	2 / 187 (1.07%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 186 (0.54%)	3 / 192 (1.56%)	2 / 187 (1.07%)
occurrences (all)	2	6	2
Chest Pain			
subjects affected / exposed	2 / 186 (1.08%)	0 / 192 (0.00%)	3 / 187 (1.60%)
occurrences (all)	2	0	3
Fatigue			

subjects affected / exposed	12 / 186 (6.45%)	13 / 192 (6.77%)	7 / 187 (3.74%)
occurrences (all)	13	13	8
Pyrexia			
subjects affected / exposed	1 / 186 (0.54%)	3 / 192 (1.56%)	2 / 187 (1.07%)
occurrences (all)	1	4	2
Irritability			
subjects affected / exposed	1 / 186 (0.54%)	4 / 192 (2.08%)	4 / 187 (2.14%)
occurrences (all)	2	5	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 186 (0.54%)	1 / 192 (0.52%)	2 / 187 (1.07%)
occurrences (all)	1	1	3
Dyspnoea			
subjects affected / exposed	1 / 186 (0.54%)	2 / 192 (1.04%)	2 / 187 (1.07%)
occurrences (all)	2	2	2
Nasal Congestion			
subjects affected / exposed	2 / 186 (1.08%)	0 / 192 (0.00%)	3 / 187 (1.60%)
occurrences (all)	2	0	3
Pharyngolaryngeal Pain			
subjects affected / exposed	1 / 186 (0.54%)	4 / 192 (2.08%)	1 / 187 (0.53%)
occurrences (all)	2	4	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 186 (0.54%)	2 / 192 (1.04%)	3 / 187 (1.60%)
occurrences (all)	2	2	3
Bradyphrenia			
subjects affected / exposed	0 / 186 (0.00%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Confusional State			
subjects affected / exposed	1 / 186 (0.54%)	2 / 192 (1.04%)	1 / 187 (0.53%)
occurrences (all)	1	2	1
Depressed Mood			
subjects affected / exposed	0 / 186 (0.00%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Depression			

subjects affected / exposed	2 / 186 (1.08%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	2	2	0
Insomnia			
subjects affected / exposed	4 / 186 (2.15%)	6 / 192 (3.13%)	4 / 187 (2.14%)
occurrences (all)	5	6	6
Nervousness			
subjects affected / exposed	2 / 186 (1.08%)	1 / 192 (0.52%)	0 / 187 (0.00%)
occurrences (all)	2	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 186 (1.08%)	3 / 192 (1.56%)	7 / 187 (3.74%)
occurrences (all)	2	3	8
Excoriation			
subjects affected / exposed	1 / 186 (0.54%)	1 / 192 (0.52%)	2 / 187 (1.07%)
occurrences (all)	1	1	3
Head Injury			
subjects affected / exposed	3 / 186 (1.61%)	1 / 192 (0.52%)	0 / 187 (0.00%)
occurrences (all)	3	1	0
Skin Laceration			
subjects affected / exposed	0 / 186 (0.00%)	1 / 192 (0.52%)	2 / 187 (1.07%)
occurrences (all)	0	1	3
Thermal Burn			
subjects affected / exposed	2 / 186 (1.08%)	0 / 192 (0.00%)	1 / 187 (0.53%)
occurrences (all)	2	0	1
Tongue Injury			
subjects affected / exposed	2 / 186 (1.08%)	0 / 192 (0.00%)	0 / 187 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Coordination Abnormal			
subjects affected / exposed	1 / 186 (0.54%)	3 / 192 (1.56%)	1 / 187 (0.53%)
occurrences (all)	2	3	1
Disturbance in Attention			
subjects affected / exposed	1 / 186 (0.54%)	3 / 192 (1.56%)	2 / 187 (1.07%)
occurrences (all)	3	3	2
Dizziness			

subjects affected / exposed	13 / 186 (6.99%)	23 / 192 (11.98%)	7 / 187 (3.74%)
occurrences (all)	19	35	8
Epilepsy			
subjects affected / exposed	4 / 186 (2.15%)	2 / 192 (1.04%)	1 / 187 (0.53%)
occurrences (all)	5	2	1
Hypoaesthesia			
subjects affected / exposed	0 / 186 (0.00%)	4 / 192 (2.08%)	1 / 187 (0.53%)
occurrences (all)	0	4	1
Headache			
subjects affected / exposed	27 / 186 (14.52%)	27 / 192 (14.06%)	25 / 187 (13.37%)
occurrences (all)	58	53	50
Memory Impairment			
subjects affected / exposed	2 / 186 (1.08%)	1 / 192 (0.52%)	1 / 187 (0.53%)
occurrences (all)	2	1	0
Migraine			
subjects affected / exposed	0 / 186 (0.00%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Paraesthesia			
subjects affected / exposed	7 / 186 (3.76%)	3 / 192 (1.56%)	2 / 187 (1.07%)
occurrences (all)	9	3	2
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 186 (0.00%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	2 / 186 (1.08%)	10 / 192 (5.21%)	8 / 187 (4.28%)
occurrences (all)	2	11	8
Tremor			
subjects affected / exposed	1 / 186 (0.54%)	1 / 192 (0.52%)	2 / 187 (1.07%)
occurrences (all)	2	1	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	2 / 187 (1.07%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Tinnitus			

subjects affected / exposed	2 / 186 (1.08%)	1 / 192 (0.52%)	0 / 187 (0.00%)
occurrences (all)	2	1	0
Vertigo			
subjects affected / exposed	3 / 186 (1.61%)	3 / 192 (1.56%)	0 / 187 (0.00%)
occurrences (all)	5	3	0
Eye disorders			
Conjunctival Haemorrhage			
subjects affected / exposed	1 / 186 (0.54%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	1	2	0
Conjunctivitis			
subjects affected / exposed	2 / 186 (1.08%)	0 / 192 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Diplopia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	2 / 187 (1.07%)
occurrences (all)	0	0	2
Vision Blurred			
subjects affected / exposed	1 / 186 (0.54%)	4 / 192 (2.08%)	2 / 187 (1.07%)
occurrences (all)	1	5	5
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	4 / 186 (2.15%)	1 / 192 (0.52%)	2 / 187 (1.07%)
occurrences (all)	4	1	2
Constipation			
subjects affected / exposed	1 / 186 (0.54%)	3 / 192 (1.56%)	3 / 187 (1.60%)
occurrences (all)	1	3	3
Dry Mouth			
subjects affected / exposed	0 / 186 (0.00%)	1 / 192 (0.52%)	2 / 187 (1.07%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	4 / 186 (2.15%)	5 / 192 (2.60%)	7 / 187 (3.74%)
occurrences (all)	9	5	8
Dyspepsia			
subjects affected / exposed	3 / 186 (1.61%)	3 / 192 (1.56%)	0 / 187 (0.00%)
occurrences (all)	4	4	0
Gastritis			

subjects affected / exposed	2 / 186 (1.08%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	2	6	0
Mouth Ulceration			
subjects affected / exposed	1 / 186 (0.54%)	2 / 192 (1.04%)	1 / 187 (0.53%)
occurrences (all)	1	4	1
Nausea			
subjects affected / exposed	11 / 186 (5.91%)	6 / 192 (3.13%)	10 / 187 (5.35%)
occurrences (all)	15	8	12
Toothache			
subjects affected / exposed	0 / 186 (0.00%)	1 / 192 (0.52%)	3 / 187 (1.60%)
occurrences (all)	0	1	3
Vomiting			
subjects affected / exposed	7 / 186 (3.76%)	2 / 192 (1.04%)	3 / 187 (1.60%)
occurrences (all)	9	2	3
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	0 / 186 (0.00%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Eczema			
subjects affected / exposed	0 / 186 (0.00%)	2 / 192 (1.04%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	1 / 186 (0.54%)	0 / 192 (0.00%)	3 / 187 (1.60%)
occurrences (all)	1	0	3
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 186 (0.00%)	2 / 192 (1.04%)	1 / 187 (0.53%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 186 (0.54%)	3 / 192 (1.56%)	0 / 187 (0.00%)
occurrences (all)	1	3	0
Back Pain			
subjects affected / exposed	2 / 186 (1.08%)	2 / 192 (1.04%)	1 / 187 (0.53%)
occurrences (all)	3	2	1
Myalgia			

subjects affected / exposed	3 / 186 (1.61%)	1 / 192 (0.52%)	3 / 187 (1.60%)
occurrences (all)	3	1	3
Musculoskeletal Pain			
subjects affected / exposed	2 / 186 (1.08%)	1 / 192 (0.52%)	1 / 187 (0.53%)
occurrences (all)	2	1	1
Pain in Extremity			
subjects affected / exposed	4 / 186 (2.15%)	3 / 192 (1.56%)	2 / 187 (1.07%)
occurrences (all)	4	3	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 186 (1.08%)	1 / 192 (0.52%)	0 / 187 (0.00%)
occurrences (all)	2	3	0
Influenza			
subjects affected / exposed	3 / 186 (1.61%)	4 / 192 (2.08%)	4 / 187 (2.14%)
occurrences (all)	5	5	4
Nasopharyngitis			
subjects affected / exposed	9 / 186 (4.84%)	6 / 192 (3.13%)	6 / 187 (3.21%)
occurrences (all)	9	7	6
Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 186 (0.00%)	0 / 192 (0.00%)	3 / 187 (1.60%)
occurrences (all)	0	0	3
Sinusitis			
subjects affected / exposed	0 / 186 (0.00%)	3 / 192 (1.56%)	0 / 187 (0.00%)
occurrences (all)	0	3	0
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 186 (2.69%)	8 / 192 (4.17%)	9 / 187 (4.81%)
occurrences (all)	7	10	10
Viral Infection			
subjects affected / exposed	0 / 186 (0.00%)	3 / 192 (1.56%)	0 / 187 (0.00%)
occurrences (all)	0	3	0
Urinary Tract Infection			
subjects affected / exposed	3 / 186 (1.61%)	2 / 192 (1.04%)	2 / 187 (1.07%)
occurrences (all)	3	2	2
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	2 / 186 (1.08%)	0 / 192 (0.00%)	1 / 187 (0.53%)
occurrences (all)	2	0	1
Anorexia			
subjects affected / exposed	1 / 186 (0.54%)	5 / 192 (2.60%)	1 / 187 (0.53%)
occurrences (all)	3	6	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2007	Amendment INT-1 included the following changes - Updated information on cases of elevated liver enzymes, reduction of the lower limit for body weight from 40 kg to 35 kg, extension of baseline platelet count and haemoglobin test value ranges, and requirement of the dosage of concomitant anti-epileptic drugs (AEDs) to be stable for at least 1 month (changed from 2 months) with no new AEDs to be added for the previous 2 months before screening. In addition, subjects with congenital short QT syndrome were now excluded and periodic use of acetaminophen up to 2,500 mg/d was now allowed throughout the study. 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 end point to be analysed sequentially. Clarification to the analysis of EuroQol 5D scores was also made. For the safety analyses, the categories for analysis of subjects with elevated liver enzyme tests were changed from 5 to 8 times the upper limit of normal (ULN) to 5 to 10 x ULN, and from >8 x ULN to >10 x ULN.
04 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 the ROW and in the countries of Europe, Australia, New Zealand, and South Africa, to meet United States and 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 and evaluation and measurement of the QTc interval using Fridericia's correction (QTcF). Analysis of additional SSQ domains, vital signs, physical and neurologic examinations, and Physician Withdrawal Check-list scores were also made.
02 November 2007	Changes were made to correct minor errors in Amendment INT-2; there were no changes made to study conduct or statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported