Clinical trial results:
An International Open-label Extension Trial to Determine Safety and Efficacy of Long-term Oral Lacosamide (SPM 927) in Patients With Partial Seizures

Summary

EudraCT number	2004-000152-16
Trial protocol	LT HU CZ FI SE ES GB
Global end of trial date	05 August 2010

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	04 June 2015

Trial information

Trial identification

Sponsor protocol code	SP0774

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00515619
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES GmbH
Sponsor organisation address	Alfred-Nobel-Str. 10, Monheim, Germany, 40789
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2010
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were:
• To obtain information about the safety of Lacosamide (LCM) following long-term exposure
• To obtain data on seizure reduction and the maintenance of efficacy by LCM during longterm exposure
• To allow subjects who had completed a LCM epilepsy study to receive LCM

Protection of trial subjects:

Not applicable

Background therapy:

Concomitant Anti-Epileptic Drug (AED) medications.

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 December 2004
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	Finland: 16
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Lithuania: 42
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Czech Republic: 50
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Croatia: 31
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Sweden: 16
Worldwide total number of subjects	376
EEA total number of subjects	314

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)	5
Adults (18-64 years)	368
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was started in December of 2004 with recruitment occurring in Australia, Croatia, Czech Republic, Finland, France, Germany, Hungary, Lithuania, Poland, Russia, Spain, Sweden, and the United Kingdom. The study had last patient last visit in August of 2010.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set, consisting of all subjects who received at least 1 dose of Lacosamide.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lacosamide

Arm description:

50 mg and 100 mg tablets of lacosamide up to 800 mg/day as twice day (BID) dosing throughout the trial (flexible dosing)

Arm type	Experimental
Investigational medicinal product name	Lacosamide
Investigational medicinal product code	SPM 927
Other name	Vimpat
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg and 100 mg tablets of lacosamide up to 800 mg/day as twice day (BID) dosing throughout the trial (flexible dosing)

Number of subjects in period 1	Lacosamide
Started	376
Completed	160
Not completed	216
Physician decision	1
Subject moved to another country	1
Fatal, Serious AE(s)	2
Subject required surgery	1
Unsatisfactory compliance	6
Site discontinuing trials	2
Fatal, Serious AE(s) and Non-Fatal, Serious AE(s)	1
Drug available on license	1

Non-Fatal, Non-Serious AE(s)	16
Consent withdrawn by subject	66
Request from sponsor	1
Pregnancy	1
Non-Fatal, Serious AE(s)	15
Lost to follow-up	4
Subject interested in other AED	1
Subject cannot attend visits	2
Lack of efficacy	92
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide
Reporting group description:	
50 mg and 100 mg tablets of lacosamide up to 800 mg/day as twice day (BID) dosing throughout the trial (flexible dosing)	

Reporting group values	Lacosamide	Total	
Number of subjects	376	376	
Age Categorical Units: Subjects			
<=18 years	7	7	
Between 18 and 65 years	366	366	
>=65 years	3	3	
Age Continuous Units: years			
arithmetic mean	37.8		
standard deviation	± 11.5	-	
Gender Categorical Units: Subjects			
Female	169	169	
Male	207	207	
Region of Enrollment Units: Subjects			
Finland	16	16	
Spain	26	26	
Lithuania	42	42	
Russian Federation	31	31	
United Kingdom	20	20	
France	10	10	
Czech Republic	50	50	
Hungary	31	31	
Poland	37	37	
Croatia	31	31	
Australia	31	31	
Germany	35	35	
Sweden	16	16	

End points

End points reporting groups

Reporting group title	Lacosamide

Reporting group description:

50 mg and 100 mg tablets of lacosamide up to 800 mg/day as twice day (BID) dosing throughout the trial (flexible dosing)

Primary: Number of subjects reporting at least 1 treatment-emergent adverse event (TEAE) during the Treatment Period (up to 5.5 years)

End point title	Number of subjects reporting at least 1 treatment-emergent adverse event (TEAE) during the Treatment Period (up to 5.5 years)[1]

End point description:

Adverse events are any untoward medical occurrences in a subject administered study treatment, whether or not these events are related to treatment.

End point type	Primary

End point timeframe:

During the Treatment Period (up to 5.5 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	376			
Units: Subjects				
Number of subjects	311			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects prematurely discontinuing due to a treatment-emergent adverse event (TEAE) during the Treatment Period (up to 5.5 years)

End point title	Number of subjects prematurely discontinuing due to a treatment-emergent adverse event (TEAE) during the Treatment Period (up to 5.5 years)[2]

End point description:

Adverse events are any untoward medical occurrences in a subject administered study treatment, whether or not these events are related to treatment.

End point type	Primary

End point timeframe:

During the Treatment Period (up to 5.5 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	376			
Units: Subjects				
Number of subjects	33			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting at least 1 serious adverse event (SAE) during the Treatment Period (up to 5.5 years)

End point title	Number of subjects reporting at least 1 serious adverse event (SAE) during the Treatment Period (up to 5.5 years)[3]

End point description:

A serious adverse event is any untoward medical occurrences in a subject administered study treatment, whether or not the event is related to treatment, with at least one of the follow outcomes: death, life-threatening, initial inpatient hospitalization or prolongation of hospitalization, significant or persistent disability/incapacity, congenital anomaly/birth defect, or an important medical event that may jeopardize the subject and require a medical/surgical intervention.

End point type	Primary

End point timeframe:

During the Treatment Period (up to 5.5 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	376			
Units: Subjects				
Number of subjects	87			

Statistical analyses

No statistical analyses for this end point

Secondary: Median percentage change from Baseline in 28-day seizure frequency during the Treatment Period (up to 5.5 years)

End point title	Median percentage change from Baseline in 28-day seizure frequency during the Treatment Period (up to 5.5 years)

End point description:

Median percentage change is the median value with respect to the percent change from Baseline across the population of subjects. Percentage change is calculated as 100 times the difference of the seizure frequency for the treatment period and the Baseline seizure frequency divided by the baseline seizure frequency.

Negative changes from Baseline indicate an improvement (i.e., a reduction) in 28-day seizure frequency.

End point type	Secondary

End point timeframe:

Baseline, Treatment Period (up to 5.5 years)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	376			
Units: Percentage change				
median (full range (min-max))				
median (full range)	-49.9 (-100 to 422.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of at least 50 % Responders during the Treatment Period (up to 5.5 years)

End point title	Percentage of at least 50 % Responders during the Treatment Period (up to 5.5 years)

End point description:

At least 50 percent response is based on the percentage reduction in 28-day seizure frequency during the Treatment Period of the open-label extension relative to the Baseline Phase of the prior study. This endpoint reflects the percentage of subjects with at least 50% reduction (ie, at least 50% change) in 28-day partial onset seizure frequency

End point type	Secondary

End point timeframe:

Treatment Period (up to 5.5 years)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	376			
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	50			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse event summaries are based on data collected during the 5.5 years of the study for all 376 patients.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Lacosamide

Reporting group description:

50 mg and 100 mg tablets of lacosamide up to 800 mg/day as twice day (BID) dosing throughout the trial (flexible dosing)

Serious adverse events	Lacosamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 376 (23.14%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm malignant			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Breast Cancer			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Ischaemia			

subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Shoulder operation			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee meniscectomy			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hospitalisation			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Therapeutic procedure			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Breast prosthesis user			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bartholin's cyst			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine polyp			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchial disorder			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Epileptic psychosis			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Aggression			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological gambling			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Weight decreased				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT corrected interval prolonged				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigation				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Head injury				
subjects affected / exposed	3 / 376 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	3 / 376 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Brain contusion				
subjects affected / exposed	3 / 376 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	3 / 376 (0.80%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	2 / 376 (0.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			

Contusion			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skeletal injury			

subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue injury			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth fracture			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Exomphalos			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	15 / 376 (3.99%)		
occurrences causally related to treatment / all	8 / 21		
deaths causally related to treatment / all	0 / 0		

Epilepsy			
subjects affected / exposed	7 / 376 (1.86%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	5 / 376 (1.33%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	3 / 376 (0.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hydrocephalus			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Coordination abnormal			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 376 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Monoparesis			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			

subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Paresis				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual field defect				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Complex partial seizures				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aura				

subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Simple partial seizures			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scotoma			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye haemorrhage			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Anal fistula				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatomegaly				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Calculus ureteric				
subjects affected / exposed	1 / 376 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hyperthyroidism				

subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibromyalgia			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Intervertebral discitis			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pilonidal cyst			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 376 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lacosamide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	232 / 376 (61.70%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	20 / 376 (5.32%)		
occurrences (all)	29		
Nervous system disorders			
Dizziness			
subjects affected / exposed	91 / 376 (24.20%)		
occurrences (all)	157		

Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all) Balance disorder subjects affected / exposed occurrences (all) Convulsion subjects affected / exposed occurrences (all)	54 / 376 (14.36%) 97 27 / 376 (7.18%) 34 23 / 376 (6.12%) 31 19 / 376 (5.05%) 25 19 / 376 (5.05%) 23		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	22 / 376 (5.85%) 25		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	31 / 376 (8.24%) 35		
Eye disorders Diplopia subjects affected / exposed occurrences (all)	51 / 376 (13.56%) 63		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	25 / 376 (6.65%) 33		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	19 / 376 (5.05%) 20		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	28 / 376 (7.45%) 38		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	52 / 376 (13.83%) 77		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2005	Protocol Amendment 2, dated 05 Apr 2005, provided for the following changes: • Change of the clinical research organization (CRO) for Data Monitoring, Drug Safety Officer, and Pharmacokineticist • Increase in the number of expected subjects and duration of the study • Clarification on the use of narcotic analgesics • Addition of Section 4.8. "Allowance for entering SPM 927 Trial SP757" • Change of Visit 10 to Week 78 (6 weeks later) and revision of telephone contacts to occur at Weeks 72, 76, 82, 86, 90, and 94 • Deletion of Visit 11 at Week 84; Visit 11 was to occur at Week 96 (previously Visit 12), Visit 12 was to occur at Week 120 (previously Visit 13), and Visit 13 was to occur at Week 144 (previously Visit 14) • Addition of visit at Week 168 (new Visit 14) and telephone contacts at Weeks 148, 152, 156, 160, 164, 172, 176, 180, 184, and 188 • Correction to the error in the heading for Section 5.5, which inadvertently omitted reference to the Termination Visit • Removal of PK assessments at Visits 12, 13, and 14, at Unscheduled Visits after Year 2, at Early Termination after Year 2 (unless the subject dropped out due to an adverse Event [AE]), and at the Final Clinic Visit • Addition of information regarding surgery as an AE and definition of life-threatening to the AE section • Provide clarification for recording AEs that increase in intensity • Addition of "worsening" as an AE outcome • Remove drop-outs due to AEs from the list of immediately reportable adverse Events (IRAEs) and specification of 1 exception to this rule • Slight modification to the cardiac conduction abnormality IRAE • Addition of Section 7.1.3.8. "Pregnancy during trial participation" • Addition of kit number to bottle label • Change in the dictionary used for coding of AEs from World Health Organization-Adverse Reaction Terms to Medical Dictionary for Regulatory Activities (MedDRA®) • Minor administrative changes
19 May 2006	Protocol Amendment 3, dated 19 May 2006, provided for the following changes: • The physical address for SCHWARZ BIOSCIENCES, GmbH was changed in the address for study personnel • Contact information for the Clinical Program Director was changed • Contact information for the Clinical Trial Statistician was changed • Contact information for the Clinical Program Medical Scientist was changed • The title and contact information for the Drug Safety Officer was changed • Additional specifications concerning withdrawal criteria regarding cardiac function were included • The title and contact information for the Safety Monitor were changed

17 March 2008	Protocol Amendment 4, dated 17 Mar 2008, provided for the following changes: • Contact information for the Associate Medical Director (Medical Therapeutics) and Associate Medical Director (Drug Safety) were added to Section 7.1.3.5, Re-exposure • Section 7.2, Laboratory measurements. In the urinalysis column in the table, albumin was changed to protein, and acetone was changed to ketones to be consistent with terminology in the clinical database • The information in Section 7.4.2, Sample labeling, was changed from "must" be filled in on all labels to "may" be filled in on all labels • Kit number in Section 8.1, Manufacturing, packaging, and labeling, was changed to Kit number (ie, bottle number) • Reference to the Per-Protocol Set in Section 11, Statistics, was removed • In Section 11.1.2, text was revised to accurately state that 1 of the safety variables was changes in 12-lead ECG instead of changes in vital sign measurements. Vital sign measurements are still listed as a safety variable • The CRF numbers were added as a way to identify data in Section 12.5, Subject privacy • The Schedule of Trial Procedures was updated to reflect the removal of the requirement to perform LCM plasma sampling after Year 2 if a subject discontinued due to an AE • The footnote in the Schedule of Trial Procedures describing the Early Termination Visit was updated • The Schedule of Trial Procedures was updated to include the additional visits associated with the additional year of the study • The individuals in Section 16.1, Declarations and signatures of persons responsible for the study, were updated
17 March 2008	Protocol Amendment 4, dated 17 Mar 2008, provided for the following changes: • The name of the study management and monitoring CRO and the vendor for central ECG services was updated • The title and contact information for the Clinical Project Manager was changed. In addition, the title of the Clinical Program Medical Scientist changed, and clarification was added to the title of the Associate Medical Director. Updates to job titles within SCHWARZ were made throughout the document. Finally, the email addresses of all SCHWARZ contacts were changed • The name of the vendor providing Central ECG Services was updated • The list of abbreviations was updated to no longer include Per-Protocol Set (PPS) • Throughout the protocol, the maximum duration of a subject's study participation was changed from 4 years to approximately 5 years, or until LCM is otherwise (eg, commercially) available, whichever is earlier • Section 2, Background information, a reference to the most recent Investigator's Brochure was added • Language was added to clarify that blood sampling for LCM plasma concentrations only needed to be performed through Year 2. Language stating that plasma sampling was necessary after Year 2, if a subject discontinued due to an AE, was deleted • The description of study medication was clarified to note that the tablets were provided in strengths rather than doses of 50 mg and 100 mg • Language was added to Section 4.6, Concomitant medications/treatments, to clarify that in general, it is no longer necessary to discontinue LCM for subjects undergoing surgery, although, it is still essential that each case be discussed on a case-by-case basis with the SCHWARZ Associate Medical Director • Treatment procedures for the new visits added by extending the duration of the study to 5 years were added to Section 5, Treatment procedures by visit • Clarification was added to the definition of a serious adverse event

08 January 2009	Protocol Amendment 5 dated 08 Jan 2009, provided for the following changes: • Contact information for the data management CRO was changed • The title and contact information for the Medical Director (Medical Therapeutics) was changed • Additional detail was added regarding bioanalytics, including a new vendor • The vendor and contact information for central ECG services was changed • The duration of the study was modified to include "or until the sponsor closes the trial" as an option for conclusion of the study. In addition, information regarding procedures that will be followed if LCM is not commercially available in a subject's country at the time the sponsor closes the trial was added • Information was added regarding procedures to follow for subjects completing the study who continue on LCM • Instructions for taper of study medication (if a subject withdraws during the trial) were placed in a new section (Section 4.4.2, Taper of trial medication) • A new section was added (Section 4.4.3, Trial completion) describing the procedures to follow for subjects who choose to continue on LCM and for subjects who choose not to continue on LCM • Section 5.5, Early Termination/Termination Visit was changed to Early Termination Visit and a new section, Section 5.6, Termination Visit, was added. Assessments to be conducted or the Early Termination Visit did not change. Assessments to be conducted at the Termination Visit were added • Contact information for the SCHWARZ Safety Scientist was changed • The classification of protocol deviations was revised to be consistent with ICH E3 • Table 1, Table 2, and Table 3 were updated to reflect the changes to the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24275520