Clinical trial results:
A Multicenter, Open-label Extension Trial to Assess the Long-term Use of Lacosamide Monotherapy and Safety of Lacosamide Monotherapy and Adjunctive Therapy in Subjects with Partial-onset Seizures

Summary

EudraCT number	2007-005440-25
Trial protocol	GB IE ES AT DK PT IT FR DE Outside EU/EEA
Global end of trial date	10 December 2014

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	03 June 2015

Trial information

Trial identification

Sponsor protocol code	SP0904

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00530855
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES INC
Sponsor organisation address	8010 ARCO CORPORATE DRIVE, RALEIGH, United States, 27617
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	23 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this trial are to:
• Obtain information about the percentage of subjects who remain on LCM monotherapy, and the duration of LCM monotherapy treatment.
• Obtain information about the long-term safety of LCM when used as monotherapy or adjunctive therapy in subjects with partial-onset seizures.

Protection of trial subjects:

None specified in the protocol except Investigator site’s usual practice and consideration to minimize patient distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	20 February 2008
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	Australia: 16
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 250
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	322
EEA total number of subjects	42

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)	3
Adults (18-64 years)	306
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Multicenter, Open-Label Study started to enroll Subjects in February 2008.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set, which is defined as all subjects who met the inclusion/exclusion criteria, signed an informed consent form, and took at least 1 dose of Trial medication.

Period 1

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

Arms

Arm title	Lacosamide

Arm description:

Lacosamide tablets for dosing 100 -800 mg/day

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

Dosage and administration details:

50 mg and 100 mg Lacosamide tablets taken for 50 -400 mg twice daily dosing for up to 2 years

Number of subjects in period 1	Lacosamide
Started	322
Completed	210
Not completed	112
Fatal Serious AE	3
Consent withdrawn by subject	30
Unsatisfactory compliance of subject	11
Lost to follow-up	9
Non Fatal Serious AE	7
Other reason for premature termination	17
Lack of efficacy	20
Non Fatal Non Serious AE	12
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide
Reporting group description:	
Lacosamide tablets for dosing 100 -800 mg/day	

Reporting group values	Lacosamide	Total	
Number of subjects	322	322	
Age Categorical Units: Subjects			
<=18 years	8	8	
Between 18 and 65 years	301	301	
>=65 years	13	13	
Age Continuous Units: years			
arithmetic mean	40.7		
standard deviation	± 13.3	-	
Gender Categorical Units: Subjects			
Male	161	161	
Female	161	161	
Race/Ethnicity, Customized Units: Subjects			
White	258	258	
Black or African American	46	46	
Asian	1	1	
Other	17	17	

End points

End points reporting groups

Reporting group title	Lacosamide
Reporting group description:	
Lacosamide tablets for dosing 100 -800 mg/day	

Primary: Percentage of Subjects on Lacosamide (LCM) Monotherapy at any time between Visit 1 and End of Study

End point title	Percentage of Subjects on Lacosamide (LCM) Monotherapy at any time between Visit 1 and End of Study[1]
End point description:	
Percentage of Subjects on Lacosamide (LCM) Monotherapy at any time between Visit 1 and End of Study.	
End point type	Primary
End point timeframe:	
From Visit 1 to End of Study (approximately 2 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	322			
Units: Participants				
Total LCM Monotherapy	292			

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Lacosamide (LCM) Monotherapy Treatment From Visit 1 to End of Study

End point title	Duration of Lacosamide (LCM) Monotherapy Treatment From Visit 1 to End of Study[2]
End point description:	
Duration of total Lacosamide Monotherapy From Visit 1 to End of Study.	
End point type	Primary
End point timeframe:	
From Visit 1 to End of Study (approximately 2 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	322			
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	479.1 (± 271.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of At Least One Treatment-Emergent Adverse Event (TEAE) From Visit 1 to End of Study

End point title	Occurrence of At Least One Treatment-Emergent Adverse Event (TEAE) From Visit 1 to End of Study

End point description:

A TEAE is defined as any untoward medical occurrence (eg, noxious or pathological changes) in a subject or clinical investigation subject compared with pre-existing conditions, that occurs during any phase of a clinical trial including Pretreatment, Run-In, Wash-Out, or Follow-Up Phases.
An TEAE is defined as being independent of assumption of any causality (eg, to trial or concomitant medication, primary or concomitant disease, or trial design).

End point type	Secondary

End point timeframe:

From Visit 1 to End of Study (approximately 2 years)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	322			
Units: Participants				
Participants	296			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Treatment-Emergent Adverse Events (TEAE) Leading to Subject Withdrawal From Visit 1 to End of Study

End point title	Occurrence of Treatment-Emergent Adverse Events (TEAE) Leading to Subject Withdrawal From Visit 1 to End of Study

End point description:

End point type	Secondary

End point timeframe:

From Visit 1 to End of Study (approximately 2 years)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	322			
Units: Participants				
Subject Withdrawal due to TEAE	22			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Study Start (Visit 1) until the End of Study (up to 2 years).

Adverse event reporting additional description:

Adverse Events refer to the Safety Set, which is defined as all subjects who met the inclusion/exclusion criteria, signed an informed consent form, and took at least 1 dose of Trial medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Lacosamide

Reporting group description:

Lacosamide tablets for dosing 100 -800 mg/day

Serious adverse events	Lacosamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 322 (17.39%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer stage II			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervix carcinoma			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon neoplasm			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic squamous cell carcinoma			

subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden unexplained death in epilepsy			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chest pain			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			

subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postictal psychosis			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electroencephalogram			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Heart rate decreased			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	2 / 322 (0.62%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Cervical vertebral fracture			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary contusion			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			

subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Congestive cardiomyopathy			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			

subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac tamponade			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	17 / 322 (5.28%)		
occurrences causally related to treatment / all	6 / 19		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	4 / 322 (1.24%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	3 / 322 (0.93%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Postictal state			
subjects affected / exposed	2 / 322 (0.62%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Complicated migraine			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyskinesia				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 322 (0.31%)			
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 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			

subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 322 (0.31%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tubo-ovarian abscess				

subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 322 (0.31%)		
occurrences causally related to treatment / all	1 / 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	238 / 322 (73.91%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	25 / 322 (7.76%)		
occurrences (all)	49		
Fall			
subjects affected / exposed	31 / 322 (9.63%)		
occurrences (all)	44		
Laceration			
subjects affected / exposed	22 / 322 (6.83%)		
occurrences (all)	32		
Nervous system disorders			
Dizziness			
subjects affected / exposed	89 / 322 (27.64%)		
occurrences (all)	142		
Headache			
subjects affected / exposed	55 / 322 (17.08%)		
occurrences (all)	81		
Convulsion			
subjects affected / exposed	29 / 322 (9.01%)		
occurrences (all)	42		
Tremor			

subjects affected / exposed occurrences (all)	26 / 322 (8.07%) 30		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 40 / 322 (12.42%) 44		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 46 / 322 (14.29%) 68 27 / 322 (8.39%) 37 23 / 322 (7.14%) 27		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 20 / 322 (6.21%) 31		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	 24 / 322 (7.45%) 26 20 / 322 (6.21%) 24 17 / 322 (5.28%) 21		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain	 31 / 322 (9.63%) 41		

subjects affected / exposed occurrences (all)	17 / 322 (5.28%) 18		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 45 / 322 (13.98%) 53 38 / 322 (11.80%) 53 20 / 322 (6.21%) 30 19 / 322 (5.90%) 23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2007	Protocol Amendment 1 dated 18 Oct 2007 provided the following key changes. Based on the date of the amendment, 26 subjects were enrolled at the time of the amendment. A clinic visit (scheduled or unscheduled) was added as a requirement for all LCM dose increases. This requirement was added because it was expected that a number of subjects entering SP904 would have been titrating to find their optimal LCM dose based on having recently met an exit criterion for SP902, and it would have been important for these subjects to increase their dose at clinic visits so that LCM tolerability was appropriately assessed. Text was added to Section 4.6 to clarify that if concomitant narcotic use became necessary, the investigator should have contacted the medical monitor to determine whether the subject should have continued participation in the study. A sentence was added to Section 4.6 stating that the use of vigabatrin, felbamate, and ethosuximide was prohibited throughout the study. This sentence was added because subjects taking vigabatrin, felbamate, and ethosuximide do not reflect an appropriate population for this study. The remainder of the changes in this amendment were minor or administrative.
26 September 2008	Protocol Amendment 2 dated 26 Sep 2008 provided the following key changes. Based on the date of the amendment, 66 subjects were enrolled at the time of the amendment. Throughout the clinical study protocol, information on the maximum duration of a subject's study participation was clarified to be 2 years after Visit 1 in SP904, and if LCM was not available (eg, commercially) in a subject's country 2 years after Visit 1 in SP904, access to LCM was to be ensured according to local laws. Criteria for withdrawal (Section 4.3.3) were differentiated into those requiring discontinuation and those that may have required discontinuation. Section 4.6 was modified to clarify when concomitant benzodiazepine use was permitted. The remainder of the changes in this amendment were minor or administrative.

21 January 2010	Protocol Amendment 3 dated 21 Jan 2010 provided the following key changes. Based on the date of the amendment, 23 subjects were enrolled at the time of the amendment. Detail was added to the protocol to allow subjects who, in consultation with the investigator, choose to initiate treatment with commercially available LCM upon completion of or withdrawal from the study, to do so without taper. The ECG- and cardiac-related withdrawal criteria and liver function test (LFT) withdrawal criteria were revised across LCM studies to reflect the sponsor's current understanding of the safety profile of LCM based on a comprehensive review of the data from clinical studies. Vagus nerve stimulation was added as a permitted concomitant treatment; subjects receiving VNS were deemed appropriate to include in the study. The AEs of special interest were revised to reflect the sponsor's current understanding of the potential risks of LCM based on a comprehensive review of the data from clinical studies and commitments to regulatory agencies. Lacosamide has been classified as a controlled substance in the USA; thus, it was necessary to add a statement that the LCM label indicated class scheduling as a controlled substance. The remainder of the changes in this amendment were minor or administrative.
04 August 2010	Protocol Amendment 4 dated 04 Aug 2010 provided the following key changes. Based on the date of the amendment, 43 subjects were enrolled at the time of the amendment. Based on the recent publication of French et al (2010) noting a revised historical control exit rate (0.653)relative to the French et al (2005) draft of the White Paper (0.678), the historical control exit rate and sample size were updated. The remainder of the changes in this amendment were minor or administrative.
07 January 2011	Protocol Amendment 5 dated 07 Jan 2011 provided the following key change. Based on the date of the amendment, 42 subjects were enrolled at the time of the amendment. The primary purpose of this protocol amendment was to revise withdrawal criteria and follow-up recommendations for abnormal LFTs. The rationale for this change is described below. The decision to reinsert additional withdrawal criteria and follow-up recommendations for abnormal LFTs was based on the following: 1. Newly adopted Food and Drug Administration (FDA) Guidance on Drug Induced Liver Injury (Jul 2009) and a recommendation from the US FDA to reinsert previously included wording regarding additional withdrawal criteria and follow-up recommendations for abnormal LFTs in LCM protocols. 2. Although no new liver-related safety issues with LCM were identified, LFT abnormality was added as a postmarketing adverse drug reaction in the LCM Company Core Data Sheet, and the EU Summary of Product Characteristics. Therefore, LCM protocols were amended to reflect this addition. With these revisions, liver-related safety signals continued to be detected via protocol-directed monitoring and additional follow-up in ongoing and future LCM clinical studies. The remainder of the changes in this amendment were minor or administrative.

20 July 2011	Protocol Amendment 6 dated 20 Jul 2011 provided the following key changes. Based on the date of the amendment, 122 subjects were enrolled at the time of the amendment. The primary purposes of this protocol amendment were to revise the exclusion criterion related to a history of suicidality, add a withdrawal criterion related to suicidality, add a list of anticipated serious AEs (SAEs), and add a third category of AEs to be reported immediately on occurrence. The rationale for these changes is described below. As recommended by the US FDA, the Columbia-Suicide Severity Rating Scale (C-SSRS) was added to evaluate and identify subjects at risk for suicide while participating in a clinical study of a drug with central nervous system activity (FDA, Guidance for Industry and Investigator, 2010). A list of anticipated SAEs was included in this amendment in compliance with the recent US FDA guidance on safety reporting requirements for studies conducted under an open Investigational New Drug application (effective 28 Mar 2011; FDA, Guidance for Industry and investigators, 2010). To meet the requirements of safety reporting and for consistency with the safety reporting currently being done for LCM "suspected transmission of an infectious agent via a medicinal product" was included as a further category of AEs to be reported immediately on occurrence. The remainder of the changes in this amendment were minor or administrative.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported