Clinical trial results:
A Historical-controlled, Multicenter, Double-blind, Randomized Trial to Assess the Efficacy and Safety of Conversion to Lacosamide 400 mg/day Monotherapy in Subjects with Partial-onset Seizures

Summary

EudraCT number	2007-005439-27
Trial protocol	GB IE ES AT DK PT IT FR DE
Global end of trial date	06 December 2012

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	SP0902

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00520741
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	18 February 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to demonstrate the efficacy and safety of conversion to LCM 400 mg/day monotherapy for partial-onset seizures (with or without secondary generalization) in subjects 16 to 70 years of age who are withdrawn from 1 to 2 marketed Anti-epileptic Drug (AEDs).

Protection of trial subjects:

Usual and customary measures to minimize discomfort for study blood testing procedures.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	02 August 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 332
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	425
EEA total number of subjects	56

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)	4
Adults (18-64 years)	408
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 160 sites in the United States of America (USA), Canada, Europe, and Australia.The maximum duration of a subject's trial participation is 30 weeks.
The Participant Flow refers to the Safety Set (SS) population which consists of all patients who received at least one dose of study medication.

Pre-assignment

Screening details:

Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.
One subject was randomized at 2 sites and excluded from the Safety Set.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Lacosamide 300 mg/day

Arm description:

Lacosamide 300 mg/dayLacosamide : 50 mg and 100 mg tablets provided for 150 mg twice daily dosing for up to 20 weeks.Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.

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 tablets provided for 200 mg twice daily dosing for up to 20 weeks
- 50 mg and 100 mg tablets provided for 150 mg twice daily dosing for up to 20 weeks

Arm title	Lacosamide 400 mg/day

Arm description:

Lacosamide 400 mg/dayLacosamide : 50 mg and 100 mg tablets provided for 200 mg twice daily dosing for up to 20 weeks.Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.

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 tablets provided for 200 mg twice daily dosing for up to 20 weeks
- 50 mg and 100 mg tablets provided for 150 mg twice daily dosing for up to 20 weeks

Number of subjects in period 1	Lacosamide 300 mg/day	Lacosamide 400 mg/day
Started	106	319
Completed	69	194
Not completed	37	125
AE, serious fatal	-	3
Other reasons for premature termination	-	6
Consent withdrawn by subject	-	11
Unsatisfactory compliance of subject	4	3
AE, non-serious non-fatal	16	44
Lost to follow-up	4	4
SAE, non-fatal	-	8
Lack of efficacy	11	30
Protocol deviation	2	15
SAE, non-fatal + AE, non-serious non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide 300 mg/day
Reporting group description:	
Lacosamide 300 mg/dayLacosamide : 50 mg and 100 mg tablets provided for 150 mg twice daily dosing for up to 20 weeks.Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.	
Reporting group title	Lacosamide 400 mg/day
Reporting group description:	
Lacosamide 400 mg/dayLacosamide : 50 mg and 100 mg tablets provided for 200 mg twice daily dosing for up to 20 weeks.Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.	

Reporting group values	Lacosamide 300 mg/day	Lacosamide 400 mg/day	Total
Number of subjects	106	319	425
Age Categorical Units: Subjects			
<=18 years	3	7	10
Between 18 and 65 years	99	303	402
>=65 years	4	9	13
Age Continuous Units: years			
arithmetic mean	41.4	40.4	
standard deviation	± 14.3	± 12.5	-
Gender Categorical Units: Subjects			
Female	50	169	219
Male	56	150	206
Race/Ethnicity, Customized Units: Subjects			
White	91	246	337
Black	9	53	62
Asian	0	1	1
Other	6	19	25
Height Units: centimeter			
arithmetic mean	169.72	169.01	
standard deviation	± 10.69	± 10.87	-
Weight Units: kilogram			
arithmetic mean	81.62	82.13	
standard deviation	± 19.53	± 21.3	-
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	28.22	28.67	
standard deviation	± 5.74	± 6.64	-
Average Baseline Seizure Frequency per 28 days Units: seizures/28 days			

arithmetic mean	10.1	10.22	
standard deviation	± 8.82	± 8.88	-

End points

End points reporting groups

Reporting group title	Lacosamide 300 mg/day

Reporting group description:

Lacosamide 300 mg/dayLacosamide : 50 mg and 100 mg tablets provided for 150 mg twice daily dosing for up to 20 weeks.Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.

Reporting group title	Lacosamide 400 mg/day

Reporting group description:

Lacosamide 400 mg/dayLacosamide : 50 mg and 100 mg tablets provided for 200 mg twice daily dosing for up to 20 weeks.Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.

Subject analysis set title	Lacosamide 400 mg/Day
Subject analysis set type	Full analysis

Subject analysis set description:

Lacosamide (LCM) 400 mg/day
Lacosamide : 50 mg and 100 mg tablets provided for 200 mg twice daily dosing for up to 20 weeks.
This study had a single inferential test of the primary efficacy variable for the LCM 400 mg/day treatment arm which was to be compared to an external historical control. As such, no adjustment for multiplicity was required. Additional analyses of the primary efficacy variable for the LCM 400 mg/day and LCM 300 mg/day treatment arms was for exploratory or supportive purposes only. The analysis of the LCM 300 mg/day arm is exploratory due to the 3:1 randomization ratio. Therefore the LCM 300 mg/day arm is not reported for this Outcome Measure.

Primary: Percentage of Subjects (using Kaplan-Meier) Who Are Identified As Meeting At Least 1 Pre-defined Exit Criteria By Day 112 Relative To The Start of Withdrawal of Background Antiepileptic Drug(s)

End point title	Percentage of Subjects (using Kaplan-Meier) Who Are Identified As Meeting At Least 1 Pre-defined Exit Criteria By Day 112 Relative To The Start of Withdrawal of Background Antiepileptic Drug(s)[1]

End point description:

Pre-defined exit criteria:
1. A 2-fold or greater increase in average monthly (28-day) partial seizure frequency (motor and non-motor) compared to average monthly partial seizure frequency (motor and non-motor) during the Baseline Phase
2. A 2-fold or greater increase in consecutive 2-day partial seizure frequency (motor and non-motor) versus the highest consecutive 2-day partial seizure frequency (motor and non-motor) that occurred during the Baseline Phase.
Note: if the highest consecutive 2-day partial seizure frequency during the Baseline Phase is 1, a 2-day partial seizure frequency of ≥3 is required to meet this exit criterion
3. Occurrence of a single generalized tonic-clonic seizure if none had occurred in the 6 months prior to randomization
4. A prolongation or worsening of overall seizure duration, frequency, type or pattern considered by the investigator as serious enough to warrant trial discontinuation
5. Status epilepticus, or new onset of serial/cluster seizures

End point type	Primary

End point timeframe:

16 Weeks Maintenance Period (approximately 112 days)

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: Due to System limitations, a statistical analysis could not be entered.
Full results including statistical analysis of this Primary and the Secondary Variable "Percentage of Subjects (Using Kaplan-Meier) Who Are Identified as Meeting at Least 1 Pre-defined Exit Criteria by Day 112, Withdrew Due to Adverse Event (AE) or Withdrew Due to Lack of Efficacy During The Maintenance Period" are available on www.clinicaltrials.gov (NCT00520741).

End point values	Lacosamide 400 mg/Day			
Subject group type	Subject analysis set			
Number of subjects analysed	284			
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Any Exit Event During The Maintenance Period

End point title	Time to First Occurrence of Any Exit Event During The Maintenance Period

End point description:

The time to first occurrence (days) of any exit event was estimated using Kaplan-Meier methods and was based on the time from the start of the Maintenance Phase to the earliest date a subject met an exit criterion. Subjects who discontinued during the Maintenance Phase due to non-exit criteria reasons or who completed the Maintenance Phase before 112 days and did not meet an exit criterion were censored as of the last Maintenance Phase dose date. Subjects completing 112 days in the Maintenance Phase were censored as of Day 112.

End point type	Secondary

End point timeframe:

16 Weeks Maintenance Period (approximately 112 days)

End point values	Lacosamide 300 mg/day	Lacosamide 400 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	82		
Units: days				
median (full range (min-max))				
days	39 (1 to 80)	45 (3 to 102)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects (using Kaplan-Meier) Who are Identified as Meeting at Least 1 Pre-defined Exit Criteria by Day 112, Withdrew due to Adverse Event (AE) or Withdrew due to Lack of Efficacy During The Maintenance Period

End point title	Percentage of Subjects (using Kaplan-Meier) Who are Identified as Meeting at Least 1 Pre-defined Exit Criteria by Day 112, Withdrew due to Adverse Event (AE) or Withdrew due to Lack of Efficacy During The Maintenance Period

End point description:

Subjects were classified as having an exit event if they experienced at least 1 of the following events

during the Maintenance Phase as of Day 112:
1. Met at least 1 exit criterion based on the calculations applied for the Primary Efficacy Analysis
2. Withdrawal due to AE with onset during the Maintenance Phase
3. Withdrew prematurely due to lack of efficacy during the Maintenance Phase

The date the subject experienced the event was set to the earliest date the subject met an exit criterion or the date of the last Maintenance Phase dose for subjects not meeting an exit criterion but withdrawing due to an AE or lack of efficacy.

The secondary analysis is only conducted on the Lacosamide 400 mg/day group.

End point type	Secondary

End point timeframe:

16 Weeks Maintenance Period (approximately 112 days)

End point values	Lacosamide 400 mg/Day			
Subject group type	Subject analysis set			
Number of subjects analysed	284			
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	32.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Monotherapy Treatment During the Monotherapy Phase of The Maintenance Period (Visit 9 - Visit 12)

End point title	Duration of Monotherapy Treatment During the Monotherapy Phase of The Maintenance Period (Visit 9 - Visit 12)

End point description:

Days on Monotherapy Treatment were defined as the number of days during the Monotherapy Phase when the subject took Lacosamide (LCM) only (ie, the total number of days exposed to LCM during the Monotherapy Phase minus any days where a concomitant or rescue Anti-epileptic Drug (AED) was taken by the subject). The days on Monotherapy Treatment did not need to be consecutive.

End point type	Secondary

End point timeframe:

Visit 9 - Visit 12 (approximately 10 weeks)

End point values	Lacosamide 300 mg/day	Lacosamide 400 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	254		
Units: days				
median (full range (min-max))				
days	71 (1 to 100)	71 (2 to 105)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Change (CGIC) From Baseline To Last Visit

End point title	Clinical Global Impression of Change (CGIC) From Baseline To Last Visit

End point description:

For the assessment of the Clinical Global Impression of Change (CGIC), the investigator should provide his/her assessment of the subject's clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status. He was asked the following:Please check the number that best describes the subject's condition over the past 4 weeks compared to Baseline:
1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

End point type	Secondary

End point timeframe:

Baseline; Last Visit (approximately 27 weeks)

End point values	Lacosamide 300 mg/day	Lacosamide 400 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	284		
Units: participants				
Very much improved	21	56		
Much improved	33	116		
Minimally improved	18	42		
No change	8	18		
Minimally worse	6	16		
Much worse	8	23		
Very much worse	1	1		
Not done	4	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's Global Impression of Change (PGIC) From Baseline To Last

Visit

End point title	Patient's Global Impression of Change (PGIC) From Baseline To Last Visit

End point description:

For the assessment of the Patient’s Global Impression of Change, the subject should provide his/her assessment of his/her own clinical status, compared to Baseline, including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject’s functional status.The subject was asked to answer the following:
Over the past 4 weeks, how have you felt compared to before you entered this clinical trial?
(Please check the number that best describes your condition.)
1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

End point type	Secondary

End point timeframe:

Baseline; Last Visit (approximately 27 weeks)

End point values	Lacosamide 300 mg/day	Lacosamide 400 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	284		
Units: participants				
Very much improved	24	81		
Much improved	33	93		
Minimally improved	15	37		
No change	10	15		
Minimally worse	3	19		
Much worse	7	22		
Very much worse	3	3		
Not done	4	14		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from Baseline (week -8) up to the end of the study (week 22). Only Treatment-Emergent Adverse Events (TEAEs) are presented.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Lacosamide 300 mg/day

Reporting group description:

Lacosamide 300 mg/day

Lacosamide : 50 mg and 100 mg tablets provided for 150 mg twice daily dosing for up to 20 weeks.

Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.

Reporting group title	Lacosamide 400 mg/day

Reporting group description:

Lacosamide 400 mg/day

Lacosamide : 50 mg and 100 mg tablets provided for 200 mg twice daily dosing for up to 20 weeks.

Subjects were randomized 3:1 to one of two therapeutic doses of Lacosamide, 400 mg/day or 300 mg/day, to ensure a study design comparable to the historical control.

Serious adverse events	Lacosamide 300 mg/day	Lacosamide 400 mg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 106 (3.77%)	21 / 319 (6.58%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polytraumatism			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			

subjects affected / exposed	1 / 106 (0.94%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 106 (0.94%)	6 / 319 (1.88%)	
occurrences causally related to treatment / all	1 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic induced encephalopathy			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden unexplained death in epilepsy			
subjects affected / exposed	0 / 106 (0.00%)	2 / 319 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glossitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory acidosis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			

subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
subjects affected / exposed	1 / 106 (0.94%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	1 / 106 (0.94%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 106 (0.94%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 106 (0.94%)	0 / 319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 106 (0.00%)	1 / 319 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lacosamide 300 mg/day	Lacosamide 400 mg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 106 (69.81%)	215 / 319 (67.40%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 106 (17.92%)	86 / 319 (26.96%)	
occurrences (all)	26	121	
Headache			
subjects affected / exposed	21 / 106 (19.81%)	45 / 319 (14.11%)	
occurrences (all)	32	58	
Convulsion			
subjects affected / exposed	17 / 106 (16.04%)	29 / 319 (9.09%)	
occurrences (all)	22	36	
Somnolence			
subjects affected / exposed	15 / 106 (14.15%)	29 / 319 (9.09%)	
occurrences (all)	19	35	
Tremor			
subjects affected / exposed	8 / 106 (7.55%)	23 / 319 (7.21%)	
occurrences (all)	8	23	
Cognitive disorder			
subjects affected / exposed	7 / 106 (6.60%)	6 / 319 (1.88%)	
occurrences (all)	8	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 106 (11.32%)	32 / 319 (10.03%)	
occurrences (all)	14	37	
Eye disorders			
Vision blurred			
subjects affected / exposed	6 / 106 (5.66%)	19 / 319 (5.96%)	
occurrences (all)	6	25	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	13 / 106 (12.26%)	46 / 319 (14.42%)	
occurrences (all)	16	57	
Diarrhoea			

subjects affected / exposed	7 / 106 (6.60%)	21 / 319 (6.58%)	
occurrences (all)	9	22	
Vomiting			
subjects affected / exposed	2 / 106 (1.89%)	23 / 319 (7.21%)	
occurrences (all)	2	27	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 106 (3.77%)	16 / 319 (5.02%)	
occurrences (all)	5	20	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 106 (7.55%)	17 / 319 (5.33%)	
occurrences (all)	10	17	
Anxiety			
subjects affected / exposed	7 / 106 (6.60%)	11 / 319 (3.45%)	
occurrences (all)	8	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 106 (8.49%)	11 / 319 (3.45%)	
occurrences (all)	9	13	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 106 (6.60%)	28 / 319 (8.78%)	
occurrences (all)	8	30	
Upper respiratory tract infection			
subjects affected / exposed	5 / 106 (4.72%)	16 / 319 (5.02%)	
occurrences (all)	6	19	

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, 1 subject was randomized prior to this amendment. The wording "post-Baseline" was removed from the definitions of exit criteria 1 and 2 to avoid confusion since all exit criteria were defined relative to the start of the withdrawal of Background AEDs. In addition, the wording "the highest" was removed from the definition of exit criterion 2 because the assessment of exit criterion 2 was based on the earliest occurrence of a doubling in the 2-day seizure frequency during the Maintenance Phase. A sentence was added describing a calculation worksheet that was provided to site personnel to assist with the calculation of average seizure frequency for determination of whether a subject had met exit criterion 1, 2, 3, or 5 (refer to Section 6.2.1 of the protocol). Eight inclusion and exclusion criteria (inclusion criteria #6, #7, #8, and #9, and exclusion criteria #3, #6, #8, and #22) were revised to improve clarity or further define the criteria, based on the original intent. Two exclusion criteria (#11 and #12) were modified to correct omissions in the original criteria. Five exclusion criteria (#9, #10, #11, #14, and #29) were modified and two exclusion criteria (#31 and #32) were added to further exclude specific populations considered inappropriate for a conversion to monotherapy study. The criteria for withdrawal of a subject requiring a modification to the AED dose(s) between Visit 1 and Visit 5 was changed to between Visit 1 and Visit 6.
18 October 2007	If concomitant narcotic use became necessary, the investigator was instructed to contact the medical monitor; restrictions in concomitant AED or benzodiazepine use were clarified (refer to Section 4.6 of the protocol). A revision was made to clarify that 1 dose reduction was allowed once the subject had taken at least 1 dose of Maintenance Phase study medication (refer to Section 8.1.1 of the protocol). A clarification was made regarding the prediction interval for an estimate of the combined pseudo-placebo exit rate (the lower 95% prediction interval was changed to the lower limit of a 2-sided 95% prediction interval), and the statement that the 95% prediction interval for the historical control provides 95% confidence that a single repeated study would yield a pseudo-placebo exit rate of 67.8% or higher was changed to a 97.5% confidence level (refer to Section 11.1.2 of the protocol). 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, 44 subjects were randomized prior to this amendment. The secondary efficacy parameter, "duration of monotherapy treatment," was changed to "during the Monotherapy Phase." The statement regarding the Taper Phase (refer to Section 4.2 and Section 4.4.1 of the protocol) was modified to permit flexibility in the length of taper, based on discussion between the investigator and the medical monitor. Select inclusion, exclusion, and withdrawal criteria were revised (refer to Section 4.3 of the protocol). Exclusion criteria based on previous and current drug use (ie, ethosuximide, felbamate, vigabatrin) were detailed. The withdrawal criteria were differentiated into those that required subject discontinuation and those that may have resulted in subject discontinuation. The criterion for withdrawal of a subject requiring a modification to the AED dose(s) was changed from between Visit 1 and Visit 6 to between Visit 3 and Visit 6. The section on withdrawal of background AEDs was revised to allow for a slower taper of the primary background AED to ensure adequate safety for the subjects (refer to Section 4.6.1 of the protocol). The allowable window for Visit 12 was clarified to be at least 112 days between Visit 6 and Visit 12. Description of the Transition Phase was revised to clarify when reintroduction/initiation of background AEDs may begin (refer to Section 5.7 of the protocol).

26 September 2008	Text was added to indicate details regarding calculations required for the assessment of exit criteria 1 and 2 (primary variables) in the statistical analysis plan (SAP) (refer to Section 11.1.2 of the protocol). Evaluation of explanatory variables was revised to clearly specify pre-planned analyses for evaluating the influence of potential differences in Baseline demographics between the LCM 400mg/day group and the historical-control population (refer to Section 11.1.3.2 of the protocol). In the statistical analysis of secondary variables, text was revised to clarify the duration of monotherapy treatment was during the Monotherapy Phase and treatment-emergent adverse events (TEAEs) would be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC; refer to Section 11.1.4 of the protocol). A statement was added regarding the evaluation of the impact of missing values on the assessment of Primary efficacy using sensitivity analyses (refer to Section 11.1.7 of the protocol). 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, 144 subjects were randomized prior to this amendment. Text associated with primary efficacy exit criterion 1 was deleted as recommended by the Food and Drug Administration (FDA) through review of the SAP for this study. 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 exclusion and 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. Exclusion criteria regarding past use of LCM, past or current use of VNS, and suicidality were also revised to include subjects deemed appropriate for enrollment. 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. The statistical methods were updated to clarify the evaluation of efficacy data for subjects who discontinue from the study due to non-exit criteria reasons. The remainder of the changes in this amendment was 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, 203 subjects were randomized prior to this 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 changes. Based on the date of the amendment, 258 subjects were randomized prior to this amendment. The primary purposes of this protocol amendment were to modify an exclusion criterion regarding prior use of LCM, to add an exclusion criterion for known sodium channelopathy, and to revise withdrawal criteria and follow-up recommendations for abnormal LFTs. The rationales for these changes are described below. The decision to exclude subjects with prior use of LCM beyond a single iv administration for acute treatment was based on an FDA recommendation (16 Dec 2010). The decision to exclude subjects with known channelopathies, such as Brugada syndrome, from clinical studies with LCM was based on an FDA recommendation (17 Aug 2010). The basis for this recommendation was a theoretical concern that enhanced slow inactivation of sodium channels by LCM may be proarrhythmic in subjects with sodium channelopathies. The decision to reinsert additional withdrawal criteria and follow-up recommendations for abnormal LFTs was based on the following: Newly adopted FDA Guidance on Drug-Induced Liver Injury (Jul 2009) and a recommendation from the FDA to re-insert previously included wording regarding additional withdrawal criteria and follow-up recommendations for abnormal LFTs in LCM protocols.

07 January 2011	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.
22 July 2011	Protocol Amendment 6 dated 22 Jul 2011 provided the following key changes. Based on the date of the amendment, 320 subjects were randomized prior to this 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 adverse events (SAEs), and to 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 (CNS) activity (FDA, Guidance for Industry and Investigators, 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 IND (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