Clinical trial results:
A Multicenter, Open-Label Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Lacosamide (LCM) Oral Solution (Syrup) as Adjunctive Therapy in Children with Partial-Onset Seizures

Summary

EudraCT number	2011-001558-27
Trial protocol	BE Outside EU/EEA
Global end of trial date	26 August 2014

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	SP847

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00938431
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, 0049 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000402-PIP02-02
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	02 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were:

To evaluate the safety, tolerability, and pharmacokinetics (PK) of Lacosamide (LCM) when added to 1 to 3 concomitant antiepileptic drugs (AEDs) in children aged 1 month to 17 years with a diagnosis of uncontrolled partial-onset seizures.

To obtain preliminary efficacy data on seizure frequency.

Protection of trial subjects:

Informed consent was obtained from the subject's parent/legal guardian and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki. When possible or as required according to local IRB/IEC, assent was also obtained from the subject.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	04 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Belgium: 1
Worldwide total number of subjects	47
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	12
Children (2-11 years)	26
Adolescents (12-17 years)	9
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The SP847 study began recruitment in November 2009. The study ended in August 2014 with 47 subjects enrolled into the study.

Pre-assignment

Screening details:

N/A

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	Total Subjects (Safety Set)

Arm description:

The Safety Set is all subjects who signed the informed consent form and took at least 1 dose of LCM in SP847.

Arm type	Experimental
Investigational medicinal product name	Lacosamide
Investigational medicinal product code	SPM 927
Other name	VIMPAT
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Lacosamide oral solution (syrup) 8 mg/kg/day, 10 mg/kg/day, and/or 12 mg/kg/day.
Depending on the target dose, treatment duration can last up to 42 days.

Number of subjects in period 1	Total Subjects (Safety Set)
Started	47
Completed	24
Not completed	23
Non-Fatal, Non-Serious AE	17
Did Not Up Titrate to 12 mg kg/day	1
Non-Fatal, Serious AE	2
Reached Maximum Dose Early	1
Lack of efficacy	1
Dosing Compliance Issue	1

Baseline characteristics

Reporting groups	
Reporting group title	Total Subjects (Safety Set)
Reporting group description:	
The Safety Set is all subjects who signed the informed consent form and took at least 1 dose of LCM in SP847.	

Reporting group values	Total Subjects (Safety Set)	Total	
Number of subjects	47	47	
Age categorical Units: Subjects			
Age Continuous Units: years			
geometric mean	7.03		
standard deviation	± 5.12	-	
Gender Categorical Units: Subjects			
Male	23	23	
Female	24	24	
Racial Group Units: Subjects			
Asian	2	2	
Black	7	7	
White	30	30	
Other/ Mixed	8	8	
Ethnicity Units: Subjects			
Hispanic or Latino	21	21	
Not Hispanic or Latino	26	26	
Weight Units: kilograms			
geometric mean	26.6		
standard deviation	± 17.64	-	
Height Units: centimeters			
geometric mean	115.46		
standard deviation	± 31.23	-	
BMI Units: kg/m^2			
geometric mean	17.48		
standard deviation	± 3.37	-	

End points

End points reporting groups

Reporting group title	Total Subjects (Safety Set)

Reporting group description:

The Safety Set is all subjects who signed the informed consent form and took at least 1 dose of LCM in SP847.

Subject analysis set title	Total Subjects (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) is defined as all subjects from the Safety Set who have at least 1 post-Baseline seizure diary day with available data during the SP847 study.

Primary: Number of subjects that report at least one Treatment-emergent Adverse Event during the study (approximately 13 weeks)

End point title	Number of subjects that report at least one Treatment-emergent Adverse Event during the study (approximately 13 weeks)[1]

End point description:

End point type	Primary

End point timeframe:

13 weeks

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: The primary objective of study SP847 was to evaluate the safety, tolerability, and PK of lacosamide when added to 1 to 3 concomitant AEDs in children aged 1 month to 17 years with a diagnosis of uncontrolled partial-onset seizures. The safety profile of lacosamide was summarized descriptively across several safety variables. Therefore, no inferential statistics were performed in this safety study.

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants				
number	42			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in seizure frequency from Baseline to End of Treatment

End point title	Percent change in seizure frequency from Baseline to End of Treatment

End point description:

End point type	Secondary

End point timeframe:

From Baseline to End of Treatment

End point values	Total Subjects (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: percentage				
arithmetic mean (standard deviation)				
percentage	21.72 (± 94.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Caregiver Global Impression of Change score at Visit 5 (Day 27/28) or Early Termination

End point title	Caregiver Global Impression of Change score at Visit 5 (Day 27/28) or Early Termination

End point description:

For the assessment of the Caregiver Global Impression of Change, the caregiver (including parent/legal guardian) provided his/her assessment of the subject's clinical status, compared to Baseline (Visit 1), including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status.

The caregiver will be asked to 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

Note: The category of Worsened represents the sum of Minimally Worse, Much Worse, and Very Much Worse. The category of Improved represents the sum of Very Much Improved, Much Improved, and Minimally Improved.

End point type	Secondary

End point timeframe:

Visit 5 (Day 27/28) or Early Termination

End point values	Total Subjects (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: units on a scale				
Improved	38			
No Change	3			

Worsened	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Change score at Visit 5 (Day 27/28) or Early Termination

End point title	Clinical Global Impression of Change score at Visit 5 (Day 27/28) or Early Termination

End point description:

For assessment of the Clinical Global Impression of Change, the investigator provided his/her assessment of the subject's clinical status, compared to Baseline (Visit 1), including an evaluation of seizure frequency and intensity, the occurrence of AEs, and subject's functional status.

The investigator will be asked to 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

Note: The category of Worsened represents the sum of Minimally Worse, Much Worse, and Very Much Worse. The category of Improved represents the sum of Very Much Improved, Much Improved, and Minimally Improved.

End point type	Secondary

End point timeframe:

Visit 5 (Day 27/28) or Early Termination

End point values	Total Subjects (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: units on a scale				
Improved	38			
No Change	3			
Worsened	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for Lacosamide at Day 7

End point title	Plasma Ctrough values for Lacosamide at Day 7

End point description:

End point type	Secondary

End point timeframe:

Day 7

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	839.9 (± 64.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for Lacosamide at Day 28

End point title	Plasma Ctrough values for Lacosamide at Day 28

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	3886 (± 70.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for Lacosamide at Day 35

End point title	Plasma Ctrough values for Lacosamide at Day 35

End point description:

End point type	Secondary

End point timeframe:

Day 35

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	4033.8 (± 52.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for Lacosamide at Day 42

End point title	Plasma Ctrough values for Lacosamide at Day 42

End point description:

End point type	Secondary

End point timeframe:

Day 42

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	4169.5 (± 73.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for SPM 12809 at Day 7

End point title	Plasma Ctrough values for SPM 12809 at Day 7

End point description:

End point type	Secondary

End point timeframe:

Day 7

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	258.4 (± 44.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for SPM 12809 at Day 28

End point title	Plasma Ctrough values for SPM 12809 at Day 28

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	754.9 (± 21.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for SPM 12809 at Day 35

End point title	Plasma Ctrough values for SPM 12809 at Day 35

End point description:

End point type	Secondary

End point timeframe:

Day 35

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	955.1 (± 24.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Ctrough values for SPM 12809 at Day 42

End point title	Plasma Ctrough values for SPM 12809 at Day 42

End point description:

End point type	Secondary

End point timeframe:

Day 42

End point values	Total Subjects (Safety Set)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
percentage	1725.8 (± 39.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) and Serious Adverse Events (SAE) were recorded for the duration of the study (October 2009 - August 2014).

The analysis group for AEs and SAEs was the Safety Set.

Adverse event reporting additional description:

The Safety Set is comprised of all subjects who signed the informed consent form and took at least 1 dose of Lacosamide in SP847.

Subjects had the ability to report more than one event. The Serious Adverse Events and Non-serious Adverse Events sections are reported in this manner.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Total Subjects (Safety Set)

Reporting group description: -

Serious adverse events	Total Subjects (Safety Set)		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 47 (12.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal inflammation			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia viral			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 47 (2.13%)		
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	Total Subjects (Safety Set)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 47 (72.34%)		
Nervous system disorders			
Somnolence			
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	5 / 47 (10.64%)		
occurrences (all)	6		
Balance disorder			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	4		
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	5 / 47 (10.64%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	5 / 47 (10.64%)		
occurrences (all)	6		

Gait disturbance subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 10 / 47 (21.28%) 12 7 / 47 (14.89%) 10 3 / 47 (6.38%) 3		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 4 / 47 (8.51%) 4		
Infections and infestations Otitis media subjects affected / exposed occurrences (all) Pharyngotonsillitis subjects affected / exposed occurrences (all)	 3 / 47 (6.38%) 3 3 / 47 (6.38%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2009	A Single-dose Reduction and Early Termination Protocol Clarification document was attached as a supplement to the protocol. In general, this attachment clarified that if a subject had a dose reduction, he/she would have been terminated early from the study after sufficient PK data were collected. 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 liver function test (LFT) withdrawal criteria were revised to reflect the Sponsor's current understanding of the safety profile of LCM based on a comprehensive review of the data from clinical studies.
27 September 2010	The study was expanded to include approximately 25 investigational sites in the USA and Mexico, with the possibility to extend to other countries if deemed necessary. The clinic visit at Day 6 (including the overnight hospitalization) was made optional for additional subjects in Cohort 1 and for all subjects in Cohorts 2, 3, and 4; subjects in these cohorts were permitted to have all Visit 3 procedures performed during a clinic visit on Day 7. The clinic visit (including the overnight hospitalization) at Day 27 (Visit 5, if the maximum recommended dose did not exceed LCM 8mg/kg/day), Day 34 (Visit 6, if the maximum recommended dose was LCM 10mg/kg/day), or Day 41 (Visit 7, if the maximum recommended dose was LCM 12mg/kg/day) was also optional for those subjects in Cohort 1 (additional subjects), Cohorts 2, 3, and 4 who were not expected to provide urine samples for pharmacokinetic (PK) analysis (eg, subjects aged <5 years); these subjects were permitted to have all Visit 5, Visit 6, or Visit 7 procedures performed during a clinic visit on the second day of each of these scheduled visits (ie, Day 28, Day 35, or Day 42). The analysis of PK data from Cohort 1 was clarified. Subjects in Cohort 1 who did not achieve a maximum dose of LCM 8mg/kg/day because of tolerability issues, but did complete the Treatment Period (ie, the collection of blood samples for PK analysis during Visit 3 and Visit 5 [or the Early Termination Visit]) contributed toward the 6 subjects needed for the determination of the maximum recommended dose for subsequent cohorts. Completion of the Treatment Period was defined as any subject who achieved steady-state at LCM ≥4mg/kg/day and completed the Early Termination Visit or Visit 5 procedures.

13 December 2010	The primary purposes of this protocol amendment were to include an additional cohort (now designated as Cohort 5) of subjects aged ≥1 month to <2 years, to define an absolute maximum dose of LCM 600 mg/day to be received by subjects in the study, to add an exclusion criterion for known sodium channelopathy, and to revise withdrawal criteria and follow-up recommendations for abnormal Liver Function Tests (LFTs). The rationales for these changes are described below. An additional cohort (now designated as Cohort 5) of 12 subjects aged ≥1 month to <2 years was included in the study. The addition of the younger subjects in Cohort 4 (previously planned for a separate clinical study of similar design) was to permit an earlier assessment of LCM PK and determination of dosing in pediatric subjects before initiating Phase 3 pediatric studies. Based on the analysis of SP847 Cohort 1 (subjects aged ≥5 to 11 years) safety and PK data, the maximum permitted LCM dose in SP847 Cohorts 2 to 5 was LCM 12 mg/kg/day (for subjects weighing up to 50 kg) or LCM 600 mg/day (for subjects weighing >50 kg). The decision to exclude subjects with known channelopathies, such as Brugada syndrome, from clinical studies with LCM was based on a Food and Drug Administration (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.
29 July 2011	- Text was added or modified to make it clear that the maximum permitted dose in SP847 was LCM 12 mg/kg/day or LCM 600 mg/day, whichever was lower. - Columbia-Suicide Severity Rating Scale 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. - Changed from LCM oral solution 15 mg/mL to LCM oral (syrup) solution 10 mg/mL due to a quality defect related to the formation of a flake-like precipitate of LCM in the 15 mg/mL syrup. - Beginning with Visit 5 (the visit at which subject had been on LCM 8 mg/kg/day for 6 to 7 days) and for subsequent visits, the remaining subjects enrolled into SP847 were required to arrive at the clinic prior to taking their morning dose of LCM. Subjects were administered their morning LCM dose by study personnel at the clinic so that an ECG could be performed 30 minutes to 1 hour after the administration of LCM. - A list of anticipated serious adverse events was included in this amendment in compliance with the USA FDA guidance on safety reporting requirements for studies conducted under an open Investigational New Drug Application. - The exclusion criterion limiting subjects who had a history of suicide attempt, had received professional counseling for suicidal ideation, or those who were currently experiencing suicidal ideation, was deleted.
23 July 2012	The primary purpose of this protocol amendment was to reduce from 2 to 1 the required minimum total number of AEDs (current or past) to have been taken by subjects in Cohort 5 (subjects 1 month to <2 years of age). This change may have increased the number of subjects in Cohort 5 who were eligible for the study. It is possible that subjects in this youngest age range may not have received AEDs for a period of time long enough for >1 AED to have been used. In addition, the exclusion criterion limiting eligible subjects to those who were able to swallow or take food by mouth was deleted (Exclusion criterion 21). A result of this change is that subjects who had a feeding tube may have been eligible for enrollment in the study and may have received LCM oral solution via a feeding tube. Previous tests have demonstrated that the LCM oral solution is compatible with administration via a feeding tube.
05 October 2012	In the FDA's 06 Aug 2012 Request for Information regarding SP847 Protocol Amendment 5, the Agency recommended that UCB BIOSCIENCES revise inclusion criterion 6 to require the use of >1 AED as monotherapy before initiating adjunctive LCM therapy in SP847. In accordance with UCB BIOSCIENCES 29 Aug 2012 Response to Request for Information, the primary purpose of this protocol amendment was to modify inclusion criterion 6 to require for all subjects a minimum total of 2 antiepileptic drugs (AEDs) (current or past) before initiation of adjunctive treatment with LCM in SP847.

31 July 2014	The primary purposes of this protocol amendment were to update the use of the Safety Set (SS), Full Analysis Set (FAS), Evaluable Set (EVS), and Pharmacokinetic Per-Protocol Set (PK-PPS) analysis sets for evaluation of safety, efficacy, and PK variables such that they reflect the planned analyses included in the Statistical Analysis Plan (SAP). Additional changes were made to clarify study procedures and variables for consistency across the protocol, SAP, and Pediatric Investigational Plan Final Opinion. The changes included in this amendment were administrative in nature and did not impact the treatment of subjects during the course of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported