Clinical trial results:
An open-label pilot study to assess the safety of oral lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy

Summary

EudraCT number	2014-004379-22
Trial protocol	Outside EU/EEA
Global end of trial date	30 August 2011

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	27 June 2015

Trial information

Trial identification

Sponsor protocol code	SP0961

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01118949
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 48 15 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	11 November 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety of Lacosamide (LCM) in subjects with uncontrolled primary generalized tonic-clonic (PGTC) seizures with idiopathic generalized epilepsy (IGE).

Protection of trial subjects:

No specific measures in the protocol to minimize pain and distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	17 May 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	14 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	49
EEA total number of subjects	0

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)	46
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Safety Set (SS) includes all enrolled subjects who took at least 1 dose of Lacosamide (LCM).

Pre-assignment

Screening details:

Participant Flow and Baseline Characteristics refer to the Safety Set (SS).

Period 1

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

Arms

Arm title	Lacosamide

Arm description:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

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:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

Number of subjects in period 1	Lacosamide
Started	49
Completed	40
Not completed	9
Consent withdrawn by subject	4
Non-Fatal, Serious AE(s)	1
Non-Fatal, Non-Serious AE(s)	4

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide
Reporting group description:	
Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.	

Reporting group values	Lacosamide	Total	
Number of subjects	49	49	
Age Categorical			
Units: Subjects			
<=18 years	4	4	
Between 18 and 65 years	45	45	
>=65 years	0	0	
Age Continuous			
Units: years			
arithmetic mean	29.7		
standard deviation	± 10.1	-	
Gender Categorical			
Units: Subjects			
Female	36	36	
Male	13	13	
Height			
Units: centimeter (cm)			
arithmetic mean	168.08		
standard deviation	± 9.32	-	
Weight			
Units: kilogram (kg)			
arithmetic mean	77.9		
standard deviation	± 19.8	-	

End points

End points reporting groups

Reporting group title	Lacosamide

Reporting group description:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

Primary: Change in the number of seizure days with absence seizures from the Baseline Phase to the Maintenance Phase

End point title	Change in the number of seizure days with absence seizures from the Baseline Phase to the Maintenance Phase[1]

End point description:

During the study subjects kept a diary to record daily seizure activity from Visit 1 until the end of study participation. The following information has been recorded:
• Seizure type
• Seizure frequency

A negative value in change of seizure days with absence seizures shows a decrease in seizure days with absence seizures.

End point type	Primary

End point timeframe:

From Baseline Phase (Weeks 0 to 4) to Maintenance Phase (Weeks 8 to 13)

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	44			
Units: number of seizure days				
arithmetic mean (standard deviation)				
mean (standard deviation)	-0.37 (± 4.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in the number of seizure days with myoclonic seizures from the Baseline Phase to the Maintenance Phase

End point title	Change in the number of seizure days with myoclonic seizures from the Baseline Phase to the Maintenance Phase[2]

End point description:

During the study subjects kept a diary to record daily seizure activity from Visit 1 until the end of study participation. The following information has been recorded:
• Seizure type
• Seizure frequency

A negative value in change of seizure days with myoclonic seizures shows a decrease in seizure days with myoclonic seizures.

End point type	Primary

End point timeframe:

From Baseline Phase (Weeks 0 to 4) to Maintenance Phase (Weeks 8 to 13)

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	44			
Units: number of seizure days				
arithmetic mean (standard deviation)				
mean (standard deviation)	-2.19 (± 5.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase)

End point title	Changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase)

End point description:

Subjects were asked to return to the clinic on the morning of the day prior to Visit 2 and Visit 6 to begin 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. Only subjects with an evaluable EEG measurement with > 19 interpretable hours at Visit 2 and Visit 6 are included in this analysis. The general spike-wave discharges are calculated per interpretable hours.

End point type	Secondary

End point timeframe:

From Visit 2 (Week 4) to Visit 6 (Week 8)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: 1/hour				
arithmetic mean (standard deviation)				
mean (standard deviation)	-3.47 (± 55.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in count of 3 Hertz (Hz) spike-wave discharges (during waking hours) on 24-hour ambulatory Electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase)

End point title	Changes in count of 3 Hertz (Hz) spike-wave discharges (during waking hours) on 24-hour ambulatory Electroencephalogram (EEG) from Visit 2 (Baseline Phase) to Visit 6 (Maintenance Phase)

End point description:

Subjects were asked to return to the clinic on the morning of the day prior to Visit 2 and Visit 6 to begin 24-hour ambulatory EEG recordings for evaluation of spike-wave discharges. Only subjects with an evaluable EEG measurement with > 19 interpretable hours at Visit 2 and Visit 6 are included in this analysis. The 3 Hertz (Hz) spike-wave discharges are calculated per awake hours.

End point type	Secondary

End point timeframe:

From Visit 2 (Week 4) to Visit 6 (Week 8)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: 1/hour				
arithmetic mean (standard deviation)				
mean (standard deviation)	0.13 (± 2.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment emergent adverse events (TEAEs) during the 10-week Treatment Period

End point title	Number of subjects with treatment emergent adverse events (TEAEs) during the 10-week Treatment Period

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From Visit 2 (Week 4) to Visit 7 (Week 13)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: participants				
TEAEs	43			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects withdrawn from the study due to Treatment Emergent Adverse Events (TEAEs) during the 10-week Treatment Period

End point title	Number of subjects withdrawn from the study due to Treatment Emergent Adverse Events (TEAEs) during the 10-week Treatment Period

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From Visit 2 (Week 4) to Visit 7 (Week 13)

End point values	Lacosamide			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: participants				
Subject Withdrawal due to TEAE	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected up to 16 weeks from Baseline (Week 0 - Week 4) over the 3-weeks Titration Period (Week 4 - Week 7) and the 6-weeks Maintenance Period (Week 7 - Week 13) to the Final Clinic Visit at the end of Week 16.

Adverse event reporting additional description:

Adverse Events refer to the Safety Set (SS). SS includes all enrolled subjects who received at least one dose of Lacosamide.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Lacosamide

Reporting group description:

Lacosamide is supplied as 50 mg, 100 mg, 150 mg, and 200 mg tablets. Subjects will begin a Dose-Titration Phase of Lacosamide at 100 mg/day (50 mg bid, approx. 12 hours apart, once in the morning and once in the evening) for 1 week. Three (3) weekly increases will follow until the subject reaches a dosage of 200 mg/day, 300 mg/day, or 400 mg/day, as deemed clinically appropriate. The final titration will be followed by a 6-week Maintenance Phase. Subjects who complete the Maintenance Phase have the opportunity to enroll in an open-label extension study; those who do not enroll will begin a 3-week End-of-Study Phase when Lacosamide will be tapered off gradually at a recommended rate of 200 mg/day/week.

Serious adverse events	Lacosamide		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Petit mal epilepsy			
subjects affected / exposed	1 / 49 (2.04%)		
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	39 / 49 (79.59%)		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Petit mal epilepsy subjects affected / exposed occurrences (all)	 19 / 49 (38.78%) 27 8 / 49 (16.33%) 8 8 / 49 (16.33%) 8 6 / 49 (12.24%) 8 4 / 49 (8.16%) 4 4 / 49 (8.16%) 4		
General disorders and administration site conditions Gait Disturbance subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all)	 5 / 49 (10.20%) 5 6 / 49 (12.24%) 6 4 / 49 (8.16%) 5		
Eye disorders Diplopia subjects affected / exposed occurrences (all)	 4 / 49 (8.16%) 4		

Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 13 / 49 (26.53%) 15 7 / 49 (14.29%) 9		
Respiratory, thoracic and mediastinal disorders Dyspnea subjects affected / exposed occurrences (all)	 4 / 49 (8.16%) 4		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 3		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 6 / 49 (12.24%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2010	The original protocol, dated 31 Aug 2009, was amended on 02 Nov 2010; changes are described in the following subsection. Protocol Amendment 1 Changes based on the amendment that affected SP0961 included, but were not limited to: • Administrative changes included changes to the Sponsor Authorization and Study Contact Information for the Clinical Program Director and Clinical Trial Biostatistician • Increased the number of study sites from 10 to 25 • Revised the inclusion criterion for number of PGTC seizures prior to Baseline to increase the duration from 28 days to 12 weeks • Removed the inclusion criterion for number of PGTC seizures during the Baseline Phase • Added an exclusion criterion for known sodium channelopathy, such as Brugada syndrome • Revised withdrawal criteria and follow-up recommendations for abnormal liver function tests (LFTs) • The primary variable of percent change in PGTC seizure frequency per 28 days from Baseline Phase to the Maintenance Phase was removed • Clarified that the secondary variable for count of 3Hz SW discharges on 24-hour ambulatory EEG only applied to waking hours • The term "Holter monitor" was replaced by "recording device" for the 24-hour ambulatory EEG recordings • Urinalysis parameter acetone was changed to ketones • "Procedures for Data Monitoring Committee" was replaced by "DMC Charter" Based on the date of the amendment, 9 subjects were enrolled in the study prior to this amendment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported