Clinical trial results:
A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF LACOSAMIDE AS ADJUNCTIVE THERAPY FOR UNCONTROLLED PRIMARY GENERALIZED TONIC-CLONIC SEIZURES IN SUBJECTS WITH IDIOPATHIC GENERALIZED EPILEPSY

Summary

EudraCT number	2011-003100-21
Trial protocol	PT SK HU DE ES CZ BE IT PL FR BG RO Outside EU/EEA
Global end of trial date	05 June 2019

Results information

Result version number	v1
This version publication date	21 December 2019
First version publication date	21 December 2019

Trial information

Trial identification

Sponsor protocol code	SP0982

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02408523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES, Inc.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, NC 27617
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, 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-PIP03-17
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	21 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of oral lacosamide (LCM) vs placebo as adjunctive therapy for uncontrolled primary generalized tonic-clonic (PGTC) seizures in subjects with idiopathic generalized epilepsy (IGE) currently taking 1 to 3 concomitant anti-epileptic drugs (AEDs) independent of the number of prior failed AEDs

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not Applicable

Actual start date of recruitment	23 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	China: 5
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 30
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Romania: 8

Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 6
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 30
Worldwide total number of subjects	242
EEA total number of subjects	99

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)	17
Adolescents (12-17 years)	32
Adults (18-64 years)	191
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in April 2015 and concluded in May 2019.

Pre-assignment

Screening details:

The study included a 12-week Historical Baseline, a 4-week Prospective Baseline Period, a 6-week (minimum) to 24-week (maximum) Treatment Period (including a 6-week titration) and a 4-week End of Study Period.
Participant Flow refers to 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	Investigator, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants >= 50 kg.
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg).
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).

Arm type	Placebo
Investigational medicinal product name	Placebo tablet
Investigational medicinal product code	
Other name	PBO
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400mg/day for adult and pediatric participants >= 50 kg.

Investigational medicinal product name	Placebo oral solution
Investigational medicinal product code	
Other name	PBO
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg or maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).

Arm title	Lacosamide

Arm description:

Lacosamide 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants with more or equal than (>=) 50 kilograms (kg).
Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants with less than (<) 30 kg).
Lasosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2

mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).

Arm type	Experimental
Investigational medicinal product name	Lacosamide tablet
Investigational medicinal product code	SPM927
Other name	Vimpat
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Lacosamide 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400mg/day for adult and pediatric participants >= 50 kg.

Investigational medicinal product name	Lacosamide oral solution
Investigational medicinal product code	SPM927
Other name	Vimpat
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg or maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).

Number of subjects in period 1	Placebo	Lacosamide
Started	121	121
Completed	110	103
Not completed	11	18
Consent withdrawn by subject	3	1
Adverse event, non-fatal	4	10
Sponsor request	1	-
Lost to follow-up	2	3
Did not satisfy extension conditions	-	1
Protocol deviation	1	2
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants >= 50 kg. Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg). Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).	
Reporting group title	Lacosamide
Reporting group description:	
Lacosamide 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants with more or equal than (>=) 50 kilograms (kg). Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants with less than (<) 30 kg). Lasosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).	

Reporting group values	Placebo	Lacosamide	Total
Number of subjects	121	121	242
Age categorical Units: Subjects			
<=18 years	27	28	55
Between 18 and 65 years	93	92	185
>=65 years	1	1	2
Age continuous Units: years			
arithmetic mean	27.64	27.82	
standard deviation	± 12.45	± 13.13	-
Gender categorical Units: Subjects			
Male	45	55	100
Female	76	66	142

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants >= 50 kg.
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg).
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).

Reporting group title	Lacosamide

Reporting group description:

Lacosamide 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants with more or equal than (>=) 50 kilograms (kg).
Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants with less than (<) 30 kg).
Lasosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).

Subject analysis set title	Placebo (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400mg/day for adult and pediatric participants >= 50 kg.
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg).
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).
Participants formed the Full Analysis Set (FAS).

Subject analysis set title	Lacosamide (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Lacosamide 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants with more or equal than (>=) 50 kilograms (kg).
Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants with less than (<) 30 kg).
Lasosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).
Participants formed the FAS.

Subject analysis set title	Placebo (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Placebo 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400mg/day for adult and pediatric participants >= 50 kg.
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg).
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).
Participants formed the Safety Set (SS).

Subject analysis set title	Lacosamide (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Lacosamide 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants with more or equal than (>=) 50 kilograms (kg).
Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants with less than (<) 30 kg).
Lasosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2

mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).
Participants formed the SS.

Primary: Time to the second primary generalized tonic clonic (PGTC) seizure during the 24-week Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point title	Time to the second primary generalized tonic clonic (PGTC) seizure during the 24-week Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point description:

The primary efficacy variable was the time to the second primary generalized tonic clonic seizure (PGTCS) during the 24-week Treatment Period which was estimated using Kaplan-Meier (KM) methods.

Note: 1 patient from the Lacosamide (FAS) group was randomized after the 125th event and did not appear in this analysis.

End point type	Primary

End point timeframe:

During the Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	119		
Units: events	76	49		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Comparison of LCM versus Placebo was based on a Cox proportional hazards regression model with an effect for treatment, stratifying for the following combinations of study participants' Baseline PGTCS frequency and Development from interactive response technology (IRT) (<= 2 per 28 days in the Combined Baseline Period and Pediatric, <= 2 per 28 days in the Combined Baseline Period and Adult, and > 2 per 28 days in the Combined Baseline Period). The reference group was Placebo.

Comparison groups	Placebo (FAS) v Lacosamide (FAS)
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.377
upper limit	0.774

Notes:

[1] - Wald's method was used to calculate the p-value, Hazard Ratio (HR) and confidence intervals (CIs).

Secondary: Seizure freedom for primary generalized tonic clonic (PGTC) seizures during the 24-week Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point title	Seizure freedom for primary generalized tonic clonic (PGTC) seizures during the 24-week Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point description:

A seizure-free day from primary generalized tonic clonic seizures (PGTCS) was defined as a day where no PGTCS were reported in the seizure diary and PGTCS were assessed, which was estimated using Kaplan-Meier (KM) methods.

Note: 1 patient from the Lacosamide (FAS) group was randomized after the 125th event and did not appear in this analysis.

End point type	Secondary

End point timeframe:

During the Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	118		
Units: percentage of participants				
number (confidence interval 95%)	17.3 (10.3 to 24.3)	31.0 (22.4 to 39.6)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The key secondary efficacy variable was evaluated using an extended Mantel-Haenszel testing procedure. Baseline PGTCS Frequency from Combined Baseline and development (age from interactive response technology (IRT)) were calculated from IRT.

Comparison groups	Placebo (FAS) v Lacosamide (FAS)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [2]
Method	Mantel-Haenszel
Parameter estimate	KM seizure free of LCM vs Placebo
Point estimate	14.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	25.1

Notes:

[2] - Superiority of LCM vs Placebo p-value was based on a chi-square test on 1 degree of freedom.

Secondary: Time to the first primary generalized tonic clonic (PGTC) seizure during the Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point title	Time to the first primary generalized tonic clonic (PGTC) seizure during the Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point description:

The time to the first primary generalized tonic clonic seizure (PGTCS) during the 24-week Treatment Period was estimated using Kaplan-Meier (KM) methods.

Note: 1 patient from the Lacosamide (FAS) group was randomized after the 125th event and did not appear in this analysis.

End point type	Secondary

End point timeframe:

During the Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	118		
Units: events	97	79		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Comparison of LCM versus Placebo was based on a Cox proportional hazards regression model with an effect for treatment, stratifying for the following combinations of study participants' Baseline PGTCS frequency and Development from interactive response technology (IRT) (<= 2 per 28 days in the Combined Baseline Period and Pediatric, <= 2 per 28 days in the Combined Baseline Period and Adult, and > 2 per 28 days in the Combined Baseline Period). The reference group was Placebo.

Comparison groups	Placebo (FAS) v Lacosamide (FAS)
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.683
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.507
upper limit	0.921

Notes:

[3] - Wald's method was used to calculate the p-value, Hazard Ratio (HR) and confidence intervals (CIs).

Secondary: Percentage of participants with at least one adverse event (AE) as reported spontaneously by the subject and/or caregiver or observed by the investigator

End point title	Percentage of participants with at least one adverse event (AE) as reported spontaneously by the subject and/or caregiver or observed by the investigator

End point description:

An AE was any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP.

End point type	Secondary

End point timeframe:

From Visit 1 (Week -4) to End of Study Period (up to Week 36)

End point values	Placebo (SS)	Lacosamide (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	121		
Units: percentage of participants				
number (not applicable)	81.8	82.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Lacosamide

End point title	Plasma Concentrations of Lacosamide

End point description:

Lacosamide plasma concentration was expressed in micrograms per milliliter (µg/mL).

Means and standard deviation (SD) were only calculated if at least 2/3 of the concentrations were quantified at the respective timepoint. Values Below Limit of Quantification (BLQ) were replaced by value of 0 in calculations of means and SDs.

Note: 999 is a placeholder used for values that were not calculated.

End point type	Secondary

End point timeframe:

During the Treatment Period from Visit 2 (Week 0) to Visit 10 (Week 24)

End point values	Placebo (SS)	Lacosamide (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	121		
Units: ug/mL				
arithmetic mean (standard deviation)				
Visit 5, Week 6 (Titration)	999 (± 999)	8.610961 (± 3.705438)		
Visit 10, Week 24 (Maintenance)	999 (± 999)	8.074427 (± 3.948749)		
Early Termination Visit	999 (± 999)	8.138085 (± 4.913627)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Week 1 to End of Study Period (up to Week 36).

Adverse event reporting additional description:

Only non-serious TEAEs occurring above the reporting threshold of 5% of participants in any treatment group are included in this summary.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Lacosamide (SS)

Reporting group description:

Lacosamide 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400 mg/day for adult and pediatric participants with more or equal than (>=) 50 kilograms (kg).
Lacosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants with less than (<) 30 kg).
Lasosamide oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).
Participants formed the SS.

Reporting group title	Placebo (SS)

Reporting group description:

Placebo 50 mg tablets: starting with 100 mg/day at Week 1. Weekly increase in steps of 50 mg or 100 mg/day were allowed. Maximal dose 400mg/day for adult and pediatric participants >= 50 kg.
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 12 mg/kg/day for pediatric participants < 30 kg).
Placebo oral solution 10 mg/ml: starting with 2 mg/kg/day, titrations steps (1 mg/kg/day to 2 mg/kg/day; maximal dose 8 mg/kg/day for pediatric participants 30 kg to < 50 kg).
Participants formed the Safety Set (SS).

Serious adverse events	Lacosamide (SS)	Placebo (SS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 121 (6.61%)	4 / 121 (3.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			

subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 121 (1.65%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	2 / 121 (1.65%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Status epilepticus			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
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 (SS)	Placebo (SS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 121 (49.59%)	41 / 121 (33.88%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	26 / 121 (21.49%)	7 / 121 (5.79%)	
occurrences (all)	34	7	
Somnolence			
subjects affected / exposed	18 / 121 (14.88%)	17 / 121 (14.05%)	
occurrences (all)	19	17	
Headache			
subjects affected / exposed	16 / 121 (13.22%)	12 / 121 (9.92%)	
occurrences (all)	18	13	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 121 (6.61%)	6 / 121 (4.96%)	
occurrences (all)	8	6	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 121 (6.61%)	2 / 121 (1.65%)	
occurrences (all)	8	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 121 (9.09%)	7 / 121 (5.79%)	
occurrences (all)	12	7	
Vomiting			
subjects affected / exposed	7 / 121 (5.79%)	1 / 121 (0.83%)	
occurrences (all)	10	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 121 (6.61%)	4 / 121 (3.31%)	
occurrences (all)	12	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2012	Protocol Amendment 1, dated 25 Sep 2012, provided the following key changes. The primary purpose of this substantial amendment was to identify significant changes to the study design including inclusion and exclusion criteria, as well as the addition of an independent data monitoring committee (IDMC). In addition, study secondary variables were changed to more accurately represent the study design. • The protocol was updated to include randomization stratified by age at informed consent (≥12 to <18 years of age vs ≥18 years of age). This was in order to maintain balance within each treatment arm and within the existing baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) as well as to provide greater control for variability when analyzing the primary efficacy variable (time to second seizure). • An inclusion criterion was added to include study participants of normal intelligence for age in the judgment of the investigator. Exclusion criteria were added or modified to further exclude study participants who had a diagnosis of developmental delay or mental retardation or a history of status epilepticus. The rationale for adding the inclusion/exclusion criteria was that study participants with developmental delay or mental retardation are more likely to have symptomatic rather than idiopathic seizures. • The inclusion criterion regarding the lower limit body weight for male and female study participants ≥12 years of age was changed from ≥ 30kg to ≥ 50kg. This was based on the observations collected to date from pediatric PK/tolerability studies.
25 September 2012	- Continuation 1 - • The text regarding the use of benzodiazepines was revised to clarify that up to 3 marketed antiepileptic drugs (AEDs) were allowed for study inclusion provided at least 1 of the 3 AEDs was a benzodiazepine regardless of indication. The intermittent use of a benzodiazepine was permitted for epilepsy indications only and limited to 2 doses per 28 days; intermittent use for non-epilepsy indications was prohibited. The rationale for this change was based on data from SP0961 in which approximately 20% of PGTCS study participants with idiopathic generalized epilepsy (IGE) used benzodiazepines. Study participants were not excluded from the study due to benzodiazepine use unless they were using benzodiazepines intermittently for indications other than epilepsy. This change was consistent with other PGTCS studies in regards to benzodiazepine use. • The secondary efficacy endpoint time to first PGTCS during the 24-week Treatment Period was added as a key secondary endpoint as UCB considers that LCM will improve the rate of seizure freedom in this difficult-to-treat population. A gatekeeping strategy was used to control Type I error. • For the assessment of the effect of LCM on quality of life in pediatric study participants, the SP0982 protocol was updated to include the Pediatric Quality of Life Inventory™ (PedsQL). The PedsQL is widely used in epilepsy and other therapeutic areas, and allows for comparison with other diseases. In addition, the PedsQL also allows for consistency across age groups and development programs, and is available in many languages for global clinical studies. • For the assessment of neurobehavior and cognition in pediatric study participants, the SP0982 protocol was updated to include the Achenbach Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function® (BRIEF), respectively. The addition of these assessments also allows for consistency across age groups and development programs.

25 September 2012	- Continuation 2 - • To ensure study participant safety, interim assessments for safety and futility were performed using an independent data monitoring committee (IDMC) due to the novel study design and primary endpoint in this patient population. Furthermore, a minority of study participants (~10%) in SP0961 showed an increase in absence seizures that, in this uncontrolled study, could not be distinguished between the drug vs the natural course of the disease and required additional examination in the current study. • SP0982 was an event-driven study where the statistical properties were based upon the number of events, not the number of study participants as is typical in most epilepsy studies (the primary efficacy variable was time to second PGTCS). As a result, the protocol was amended to reflect this focus. Furthermore, a maximum sample size of 250 study participants was introduced if 125 events were not observed on or before the 200th study participant randomized. This is standard for event-driven studies and represents an approximate 25% increase from the projected sample size, in case the event rate was lower than anticipated.
11 July 2014	Protocol Amendment 2, dated 11 Jul 2014, provided the following key changes. The primary purpose of this substantial amendment was to identify significant changes to the study design and the inclusion of pediatric study participants (≥4 to <12 years of age). In addition, the key study secondary efficacy variable was changed to more accurately represent the study design. • The protocol was updated to include randomization stratified by age at informed consent for study participants ≥4 to <12 years of age. This was in order to maintain balance within each treatment arm and within the existing baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) as well as provide greater control for variability when analyzing the primary efficacy variable (time to second seizure). • An inclusion criterion was modified to include study participants ≥4 years of age. Exclusion criteria were modified in regards to study participants who had a diagnosis of developmental delay or mental retardation or a history of status epilepticus. The rationale for modifying the exclusion criteria was that study participants with developmental delay or mental retardation are more likely to have symptomatic rather than idiopathic seizures. The rationale for modifying the exclusion criteria for study participants with a history of status epilepticus was to align with the withdrawal criteria (ie, a study participant may have been withdrawn from the study due to an episode of status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new seizure type considered by the investigator to require intervention).
08 June 2016	Protocol Amendment 4, dated 08 Jun 2016, provided the following key changes. The primary purpose of this substantial amendment was to clarify elements of the study design including inclusion and exclusion criteria, exit criteria, and withdrawal criteria, as well as the duration of the Baseline Period, procedure for dividing the daily dose for the tablet formulation without breaking tablets, permitted and prohibited concomitant medication, consent for prescreening electroencephalogram (EEG), seizure count, temperature for storage of plasma samples, and determination of sample size. The protocol was also updated according to the new UCB protocol template, for example, with the addition of text regarding potential drug-induced liver injury (PDILI).

07 November 2017	Protocol Amendment 5, dated 07 Nov 2017, provided the following key changes. The primary purpose of this substantial amendment was to stop the study participants' study participation once 125 events had been observed to avoid exposing study participants to Placebo unnecessarily and allow for flexible dosing of the treatment in the open-label follow-up study EP0012. In addition, the following changes were made: • The initial plan was to enroll 20% pediatric study participants out of a total sample size of approximately 200 study participants, which would have resulted in 40 pediatric study participants enrolled in the study. Due to a fluctuating event rate, the study was changed to enroll study participants until the 125th event occurred (an event was defined as the occurrence of the second PGTCS during the 24-week Treatment Period). Changing the number of pediatric study participants from 20% to 40 absolute ensured that at least 40 pediatric study participants were recruited while also limiting the number of required pediatric study participants in case more than 200 study participants were enrolled. This was considered appropriate in light of the extremely challenging recruitment of pediatric study participants in this study. Additionally, from the biostatistical point of view, increasing the number of pediatric study participants from 40 to 45 or 50 is very unlikely to yield significantly new or different safety information. • To update the introduction with regulatory information on the marketing authorization of Vimpat and to provide an update on the LCM clinical program. • To appropriately align the Inclusion Criterion 7.a with the examples given in the supportive table. • To clarify that Visit 5 was the beginning of the Maintenance Period (18 weeks). • To remove some blood sampling details from the protocol and refer to the laboratory manual.
07 November 2017	- Continuation - • To clarify the potential drug-induced liver injury (PDILI) criteria requiring immediate and permanent discontinuation of the investigational medicinal product (IMP). • To clarify that if the monitor had no direct access to the source electronic medical records, certified copies should have been generated by the investigator and verified by the monitor against the original medical record. • To make a minor clarification to the sentence about pooling strategies for age strata for consistency with the Statistical Analysis Plan (SAP).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported