Clinical trial results:
A MULTI-CENTER, OPEN-LABEL, EXPLORATORY STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF LACOSAMIDE AS ADJUNCTIVE THERAPY IN SUBJECTS >=1 MONTH TO <18 YEARS WITH EPILEPSY SYNDROMES ASSOCIATED WITH GENERALIZED SEIZURES

Summary

EudraCT number	2012-001446-18
Trial protocol	DE HU PL Outside EU/EEA FR
Global end of trial date	10 April 2018

Results information

Result version number	v1 (current)
This version publication date	25 October 2018
First version publication date	25 October 2018

Trial information

Trial identification

Sponsor protocol code	SP0966

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01969851
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	25 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the safety and tolerability of lacosamide (LCM) when added to 1 to 3 concomitant antiepileptic drugs (AEDs) in pediatric subjects with epilepsy syndromes associated with generalized seizures
• To obtain preliminary efficacy data of LCM on seizure frequency in pediatric epilepsy syndromes associated with generalized seizures
• An additional objective is to evaluate the pharmacokinetic (PK) of LCM in subjects >=1 month to <18 years of age

Protection of trial subjects:

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

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	13 February 2014
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?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	55
EEA total number of subjects	28

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)	3
Children (2-11 years)	31
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in February 2014 and concluded in April 2018.

Pre-assignment

Screening details:

The Participant Flow refers to the Safety Set which consisted of all enrolled subjects who took at least 1 dose of lacosamide (LCM).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lacosamide 1 month - <4 years

Arm description:

Subjects, aged 1 month to <4 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Arm type	Experimental
Investigational medicinal product name	Lacosamide oral solution
Investigational medicinal product code	LCM oral solution
Other name	Vimpat oral solution
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The formulation of LCM to be administered is based on the weight of the subject. Subjects weighing <50 kg or those >=50 kg who are unable or unwilling to swallow tablets were dispensed LCM oral solution. Treatment was initiated with LCM oral solution at 2 mg/kg/day for subjects weighing <50 kg, or 100 mg/day in subjects weighing >=50 kg. The dose was titrated in a stepwise fashion on a weekly basis to optimize tolerability and seizure control, not to exceed 12 mg/kg/day (oral solution) for subjects weighing <50 kg. At the end of the Titration Period (Visit 6), a 12 week Maintenance Period began. Subjects had to titrate to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg in order to enter the Maintenance Period. The LCM dose remained stable throughout the Maintenance Period. Subjects who required a change in dose during the Maintenance Period were withdrawn from the study.

Arm title	Lacosamide 4 years - <12 years

Arm description:

Subjects, aged 4 years to <12 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Arm type	Experimental

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

Dosage and administration details:

The formulation of LCM to be administered is based on the weight of the subject. Subjects weighing <50 kg or those >=50 kg who are unable or unwilling to swallow tablets were dispensed LCM oral solution. Treatment was initiated with LCM oral solution at 2 mg/kg/day for subjects weighing <50 kg, or 100 mg/day in subjects weighing >=50 kg. The dose was titrated in a stepwise fashion on a weekly basis to optimize tolerability and seizure control, not to exceed 12 mg/kg/day (oral solution) for subjects weighing <50 kg. At the end of the Titration Period (Visit 6), a 12 week Maintenance Period began. Subjects had to titrate to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg in order to enter the Maintenance Period. The LCM dose remained stable throughout the Maintenance Period. Subjects who required a change in dose during the Maintenance Period were withdrawn from the study.

Investigational medicinal product name	Lacosamide tablet
Investigational medicinal product code	LCM tablet
Other name	Vimpat tablet
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The formulation of LCM to be administered is based on the weight of the subject. Only subjects weighing >=50 kg who are able and willing to swallow tablets were dispensed LCM tablets. Treatment was initiated with LCM tablets at 100 mg/day. The dose was titrated in a stepwise fashion on a weekly basis to optimize tolerability and seizure control, not to exceed 600 mg/day in subjects weighing >=50 kg. At the end of the Titration Period (Visit 6), a 12 week Maintenance Period began. Subjects had to titrate to at least 200 mg/day for subjects weighing >=50 kg in order to enter the Maintenance Period. The LCM dose remained stable throughout the Maintenance Period. Subjects who required a change in dose during the Maintenance Period were withdrawn from the study.

Arm title	Lacosamide 12 years - <18 years

Arm description:

Subjects, aged 12 years to <18 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Arm type	Experimental
Investigational medicinal product name	Lacosamide oral solution
Investigational medicinal product code	LCM oral solution
Other name	Vimpat oral solution
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

The formulation of LCM to be administered is based on the weight of the subject. Subjects weighing <50 kg or those >=50 kg who are unable or unwilling to swallow tablets were dispensed LCM oral solution. Treatment was initiated with LCM oral solution at 2 mg/kg/day for subjects weighing <50 kg, or 100 mg/day in subjects weighing >=50 kg. The dose was titrated in a stepwise fashion on a weekly basis to optimize tolerability and seizure control, not to exceed 12 mg/kg/day (oral solution) for subjects weighing <50 kg. At the end of the Titration Period (Visit 6), a 12 week Maintenance Period began. Subjects had to titrate to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg in order to enter the Maintenance Period. The LCM dose remained stable throughout the Maintenance Period. Subjects who required a change in dose during the Maintenance Period were withdrawn from the study.

Investigational medicinal product name	Lacosamide tablet
Investigational medicinal product code	LCM tablet
Other name	Vimpat tablet
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The formulation of LCM to be administered is based on the weight of the subject. Only subjects weighing >=50 kg who are able and willing to swallow tablets were dispensed LCM tablets. Treatment was initiated with LCM tablets at 100 mg/day. The dose was titrated in a stepwise fashion on a weekly basis to optimize tolerability and seizure control, not to exceed 600 mg/day in subjects weighing >=50 kg. At the end of the Titration Period (Visit 6), a 12 week Maintenance Period began. Subjects had to titrate to at least 200 mg/day for subjects weighing >=50 kg in order to enter the Maintenance Period. The LCM dose remained stable throughout the Maintenance Period. Subjects who required a change in dose during the Maintenance Period were withdrawn from the study.

Number of subjects in period 1	Lacosamide 1 month - <4 years	Lacosamide 4 years - <12 years	Lacosamide 12 years - <18 years
Started	10	24	21
Completed	9	21	14
Not completed	1	3	7
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	-	-	3
No effective dose in Titration period	-	-	1
Sponsor decision	-	-	1
Lack of efficacy	-	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide 1 month - <4 years

Reporting group description:

Subjects, aged 1 month to <4 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Reporting group title	Lacosamide 4 years - <12 years

Reporting group description:

Subjects, aged 4 years to <12 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Reporting group title	Lacosamide 12 years - <18 years

Reporting group description:

Subjects, aged 12 years to <18 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Reporting group values	Lacosamide 1 month - <4 years	Lacosamide 4 years - <12 years	Lacosamide 12 years - <18 years
Number of subjects	10	24	21
Age categorical Units: Subjects			
<=18 years	10	24	21
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age continuous Units: years			
arithmetic mean	2.716	6.969	14.753
standard deviation	± 0.765	± 1.998	± 1.766
Gender categorical Units: Subjects			
Female	0	9	15
Male	10	15	6

Reporting group values	Total		
Number of subjects	55		
Age categorical Units: Subjects			
<=18 years	55		
Between 18 and 65 years	0		
>=65 years	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	24		
Male	31		

End points

End points reporting groups

Reporting group title	Lacosamide 1 month - <4 years

Reporting group description:

Subjects, aged 1 month to <4 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Reporting group title	Lacosamide 4 years - <12 years

Reporting group description:

Subjects, aged 4 years to <12 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Reporting group title	Lacosamide 12 years - <18 years

Reporting group description:

Subjects, aged 12 years to <18 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Subject analysis set title	Lacosamide 1 month - <4 years SS
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects, aged 1 month to <4 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Subject analysis set title	Lacosamide 4 years - <2 years SS
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects, aged 4 years to <12 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Subject analysis set title	Lacosamide 12 years - <18 years SS
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects, aged 12 years to <18 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Primary: Mean changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 to Visit 6

End point title	Mean changes in count of generalized spike-wave discharges on 24-hour ambulatory electroencephalogram (EEG) from Visit 2 to Visit 6[1]

End point description:

The mean change in the count of generalized spike-wave discharges was presented. Visit 6 (Week 6) was the End of the Titration Period.

End point type	Primary

End point timeframe:

From Baseline (Day 1) to Visit 6 (Week 6)

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 as descriptive statistics only.

End point values	Lacosamide 1 month - <4 years SS	Lacosamide 4 years - <2 years SS	Lacosamide 12 years - <18 years SS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	24	21	
Units: discharges				
arithmetic mean (standard deviation)	-4.55 (± 257.32)	-166.22 (± 447.80)	-203.12 (± 432.42)	

Statistical analyses

No statistical analyses for this end point

Primary: Mean change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, partial evolving to secondarily generalized) per 28 days from the Baseline Period to the Maintenance Period (approximately 24 weeks)

End point title	Mean change in days with any generalized seizures (absence, myoclonic, clonic, tonic, tonic-clonic, atonic, partial evolving to secondarily generalized) per 28 days from the Baseline Period to the Maintenance Period (approximately 24 weeks)[2]

End point description:

The mean change in the count of days with generalized seizures was presented.

End point type	Primary

End point timeframe:

Baseline Period to the Maintenance Period (approximately 24 weeks)

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 as descriptive statistics only.

End point values	Lacosamide 1 month - <4 years SS	Lacosamide 4 years - <2 years SS	Lacosamide 12 years - <18 years SS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	23	20	
Units: days				
arithmetic mean (standard deviation)				
mean (standard deviation)	0.50 (± 6.63)	-1.90 (± 3.76)	-3.38 (± 6.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean changes in count of 3 Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 6

End point title	Mean changes in count of 3 Hz spike-wave discharges (during waking hours) on 24-hour ambulatory EEG from Visit 2 to Visit 6

End point description:

The mean change in the count of 3 Hertz (Hz) spike-wave discharges was presented. Visit 6 (Week 6) was the End of the Titration Period.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) to Visit 6 (Week 6)

End point values	Lacosamide 1 month - <4 years SS	Lacosamide 4 years - <2 years SS	Lacosamide 12 years - <18 years SS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	22	14	
Units: count of discharges				
arithmetic mean (standard deviation)				
mean (standard deviation)	-0.14 (± 0.42)	-1.60 (± 9.92)	0.00 (± 0.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subject withdrawals due to Adverse Events from Baseline to End of Study (approximately 32 weeks)

End point title	Number of subject withdrawals due to Adverse Events from Baseline to End of Study (approximately 32 weeks)

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to End of Study (approximately 32 weeks)

End point values	Lacosamide 1 month - <4 years SS	Lacosamide 4 years - <2 years SS	Lacosamide 12 years - <18 years SS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	24	21	
Units: participants	0	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects experiencing at least 1 Treatment-emergent Adverse event from Baseline to End of Study (approximately 32 weeks)

End point title	Number of subjects experiencing at least 1 Treatment-emergent Adverse event from Baseline to End of Study (approximately 32 weeks)

End point description:

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

End point type	Secondary

End point timeframe:

From Baseline to End of Study (approximately 32 weeks)

End point values	Lacosamide 1 month - <4 years SS	Lacosamide 4 years - <2 years SS	Lacosamide 12 years - <18 years SS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	24	21	
Units: participants	10	21	18	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected throughout the study (up to week 26)

Adverse event reporting additional description:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Lacosamide 1 month - <4 years

Reporting group description:

Subjects, aged 1 month to <4 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50 kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Reporting group title	Lacosamide 12 years - <18 years

Reporting group description:

Subjects, aged 12 years to <18 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Reporting group title	Lacosamide 4 years - <12 years

Reporting group description:

Subjects, aged 4 years to <12 years, who were administered Lacosamide oral solution (for subjects weighing <50 kg) or tablet (for subjects weighing >=50 kg). The initial dose of 2 mg/kg/day (for subjects weighing <50 kg), or 100 mg/day (for subjects weighing >=50 kg) was titrated to optimize tolerability and seizure control to at least 4 mg/kg/day for subjects weighing <50kg, or 200 mg/day for subjects weighing >=50 kg; not to exceed 12 mg/kg/day for subjects weighing <50 kg, or 600 mg/day in subjects weighing >=50 kg.

Serious adverse events	Lacosamide 1 month - <4 years	Lacosamide 12 years - <18 years	Lacosamide 4 years - <12 years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Lacosamide 1 month - <4 years	Lacosamide 12 years - <18 years	Lacosamide 4 years - <12 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	15 / 21 (71.43%)	19 / 24 (79.17%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	4 / 10 (40.00%)	2 / 21 (9.52%)	2 / 24 (8.33%)
occurrences (all)	4	3	2
Headache			
subjects affected / exposed	1 / 10 (10.00%)	4 / 21 (19.05%)	0 / 24 (0.00%)
occurrences (all)	6	7	0
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Convulsion			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 10 (40.00%)	3 / 21 (14.29%)	6 / 24 (25.00%)
occurrences (all)	5	3	7
Irritability			
subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	1 / 24 (4.17%)
occurrences (all)	1	1	2
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	4 / 24 (16.67%)
occurrences (all)	0	1	5

Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	2 / 21 (9.52%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 10 (10.00%)	1 / 21 (4.76%)	4 / 24 (16.67%)
occurrences (all)	1	1	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 10 (20.00%)	0 / 21 (0.00%)	2 / 24 (8.33%)
occurrences (all)	2	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 10 (50.00%)	3 / 21 (14.29%)	1 / 24 (4.17%)
occurrences (all)	7	3	1
Pharyngotonsillitis			
subjects affected / exposed	2 / 10 (20.00%)	3 / 21 (14.29%)	1 / 24 (4.17%)
occurrences (all)	2	3	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 21 (9.52%)	4 / 24 (16.67%)
occurrences (all)	0	2	4
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 21 (9.52%)	2 / 24 (8.33%)
occurrences (all)	1	3	2
Pharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 21 (4.76%)	3 / 24 (12.50%)
occurrences (all)	0	1	3
Ear infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 21 (0.00%)	2 / 24 (8.33%)
occurrences (all)	3	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 10 (20.00%)	2 / 21 (9.52%)	0 / 24 (0.00%)
occurrences (all)	2	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2012	This Amendment has been issued following a Special Protocol Assessment performed by the USA FDA on SP0969 (NCT01921205). Where applicable, the recommendations made by the FDA have been incorporated into the current protocol. Major changes: •Dosing was changed to match SP0969 (based on subject weight) •Inclusion criteria for concomitant antiepileptic drugs (AEDs) and vagus nerve stimulation (VNS) were modified to match SP0969 •Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy were excluded. The effect of lacosamide (LCM) in this population is planned to be investigated in a confirmatory study •Exclusion criteria for felbamate and vigabatrin were modified •The Behavior Rating Inventory of Executive Function was added as an additional safety assessment •The Pediatric Quality of Life Inventory was added as an additional efficacy assessment •Health care resource use was added as an efficacy variable •The requirement to measure height was restricted to visits with a complete physical examination •Withdrawal criteria based on the use of rescue medication was added •An additional assessment at end of titration was added for the Achenbach Child Behavior Checklist. •Orthostatic blood pressure and pulse assessments were added •Concomitant, prohibited and rescue medications were modified to match SP0969 •The terminology “syrup” was replaced with oral solution •Assessment time points for scales and questionnaires were modified •Additional assessments for VNS assessments and urinalysis were added •The number of sites was increased to 40 •Additional text was added clarifying which version of the Columbia Suicide Severity Rating Scale (C-SSRS) should be used at study entry and for subjects turning 6 years of age. •Administrative changes •Typographical changes

21 June 2013	The present amendment has been issued following additional feedback from the USA FDA on both SP0969 and SP0966. Where applicable, the recommendations made by the FDA have been incorporated into the current protocol. In addition, updates were made for consistency with other lacosamide (LCM) protocols. The following major changes were made: •The titration and taper schedules were changed to include different weight categories, a 600 mg/day LCM dose, and an extended (slower) titration schedule. •The schedule of assessments was modified to include the changes to the titration schedule, additional visits, and changes to the assessments at each visit. •The schematic diagrams were updated to reflect the additional changes to the titration and taper schedules. •Inclusion criteria were modified to allow inclusion of subjects with West syndrome. •Measurements of head circumference were included. •The language regarding unscheduled visits was updated to make it clear that investigators can perform additional procedures based on their judgment and medical need. •The age allowed for initial enrollment was reduced from 4 to 2 years. •The duration of the safety follow-up was made consistent with other LCM studies (SP0969). •The definition of end of study for the subjects has been clarified to account for subjects who enter and do not enter the open-label study. •Additional language was added describing the procedures if the study is completed and the taper is not required at the end of the study. •The language regarding study medication storage has been updated according to the clinical label. •The language regarding some of the scales used in this study has been updated for clarification. •The number of sites and countries in the study were increased. •Administrative changes •Typographical changes
25 February 2014	The following key changes were made throughout the protocol: •Subjects with primary generalized tonic-clonic seizures (PGTCS) with a diagnosis of idiopathic generalized epilepsy (IGE) are not excluded from the study population. •Subjects >=1 month to <2 years of age can now be enrolled into SP0966. •Subjects with second- or third-degree heart block are excluded from SP0966, without the requirement of being at rest. •The atrioventricular (AV) block withdrawal criterion was modified to second or third degree AV block, without the requirement of being awake. •Head circumference is to be measured only in subjects <4 years of age. •Administrative changes: the name and details of the Clinical Project Manager and the Serious Adverse Event (SAE) Reporting Email address were updated.
26 February 2015	The following key changes were made throughout the protocol: •Subjects with primary generalized tonic-clonic seizures with a diagnosis of idiopathic generalized epilepsy were excluded from the study population. •Exclusion criterion for creatinine clearance rate has changed from <50 milliLiters/minute (mL/min) to <30 mL/min. •Exclusion criterion number 20 has been reworded to clarify that the excluded sodium channelopathies are cardiac. •Administrative changes: the name of the Study Physician and the name of the contract research organization (CRO) have been updated, and the Sponsor Declaration has been updated for electronic signature. •Russia has been removed as a participating country.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported