Clinical trial results:
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Lacosamide as Adjunctive Therapy in Subjects With Epilepsy >=1 Month to <4 Years of Age With Partial-Onset Seizures

Summary

EudraCT number	2013-000717-20
Trial protocol	HU GB CZ LT IT DE ES FR PL RO GR BG HR SK BE PT DK FI Outside EU/EEA
Global end of trial date	28 May 2020

Results information

Result version number	v1
This version publication date	04 December 2020
First version publication date	04 December 2020

Trial information

Trial identification

Sponsor protocol code	SP0967

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02477839
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)	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	12 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2020
Global end of trial reached?	Yes
Global end of trial date	28 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of LCM administered concomitantly with 1 to 3 AEDs in subjects ≥1 month to <4 years of age with epilepsy who currently have uncontrolled partial-onset seizures.

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	05 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	China: 14
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Georgia: 21
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Mexico: 29
Country: Number of subjects enrolled	Moldova, Republic of: 2
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 1

Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	Serbia: 8
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Ukraine: 64
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	255
EEA total number of subjects	61

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)	121
Children (2-11 years)	134
Adolescents (12-17 years)	0
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 June 2015 and concluded in May 2020.

Pre-assignment

Screening details:

Completed study was defined as participants who had "Completed study participant" selected as status at termination. The total number of participants who completed the study comprises of those who completed the Transition Period and the ones that completed the Taper Period after completing the Maintenance Period.
Participant Flow refers to the SS.

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	Assessor, Carer, Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching placebo syrup.

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

Dosage and administration details:

Matching placebo syrup. Placebo was measured and administered via a dosing syringe. If a study participant was unable to swallow the oral solution, administration by feeding tube was permitted.

Arm title	Lacosamide

Arm description:

Participants received lacosamide (LCM) syrup 8 mg/kg/day to 12 mg/kg/day.

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

Dosage and administration details:

Lacosamide (LCM) syrup 8 mg/kg/day to 12 mg/kg/day. LCM was measured and administered via a dosing syringe. If a study participant was unable to swallow the oral solution, administration by feeding tube was permitted.

Number of subjects in period 1	Placebo	Lacosamide
Started	127	128
Completed Transition Period	124	117 [1]
Completed Taper after Maintenance	0 [2]	1 [3]
Completed	124	118
Not completed	3	10
Consent withdrawn by subject	3	3
Adverse event, non-fatal	-	1
Exclusion criterion	-	1
Lack of tolerability	-	1
Parents decided to stop medication	-	1
Participant had PGS during V6	-	1
Protocol deviation	-	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at the milestones reflects those who completed the Transition Period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at the milestones reflects those who completed the Taper Period after completing the Maintenance Period.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of participants at the milestones reflects those who completed the Taper Period after completing the Maintenance Period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo syrup.	
Reporting group title	Lacosamide
Reporting group description:	
Participants received lacosamide (LCM) syrup 8 mg/kg/day to 12 mg/kg/day.	

Reporting group values	Placebo	Lacosamide	Total
Number of subjects	127	128	255
Age categorical Units: Subjects			
<=18 years	127	128	255
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age continuous Units: months			
arithmetic mean	26.1	25.2	
standard deviation	± 13.4	± 13.6	-
Gender categorical Units: Subjects			
Male	75	71	146
Female	52	57	109

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received matching placebo syrup.	
Reporting group title	Lacosamide
Reporting group description: Participants received lacosamide (LCM) syrup 8 mg/kg/day to 12 mg/kg/day.	
Subject analysis set title	Placebo (SS)
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received matching placebo syrup, forming the Safety Set (SS).	
Subject analysis set title	Lacosamide (SS)
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received lacosamide (LCM) syrup 8 mg/kg/day to 12 mg/kg/day, forming the SS.	
Subject analysis set title	Placebo (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: Participants received matching placebo syrup, forming the Full Analysis Set (FAS).	
Subject analysis set title	Lacosamide (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: Participants received lacosamide (LCM) syrup 8 mg/kg/day to 12 mg/kg/day, forming the FAS.	

Primary: Percentage of participants with >= 50% reduction in partial-onset seizure frequency from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point title	Percentage of participants with >= 50% reduction in partial-onset seizure frequency from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point description:

A responder was a study participant experiencing a 50% or greater reduction in average daily frequency (ADF) of electrographic partial-onset seizures (POS) recorded on the End-of-Maintenance (EOM) Period video-electroencephalogram (EEG) compared to the End-of-Baseline (EOB) Period video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). The analysis consisted of all study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Primary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	128		
Units: percentage of participants				
number (not applicable)	37.5	41.4		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Odds ratio (LCM/PBO), 95% CI, and p-value were from a logistic regression model with factors for treatment, pooled randomized age stratum, and pooled center.	
Comparison groups	Lacosamide (FAS) v Placebo (FAS)
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5809
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.991

Primary: Participant withdrawals due to adverse events (AEs) during the study

End point title	Participant withdrawals due to adverse events (AEs) during the study[1]
End point description:	
An adverse event (AE) is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. An AE could, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication. The Safety Set (SS) included all randomized study participants who took at least 1 dose of study medication.	
End point type	Primary
End point timeframe:	
From the Baseline Period (Day -7) to the End of Study Visit (up to 93 days)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this outcome. Results were summarized as descriptive statistics only.

End point values	Placebo (SS)	Lacosamide (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	128		
Units: percentage of participants				
number (not applicable)	0	1.6		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with adverse events reported spontaneously by the participant's parent(s) and/or legal representative(s)/caregiver(s) (in accordance with local regulation) or observed by the investigator

End point title	Percentage of participants with adverse events reported spontaneously by the participant's parent(s) and/or legal representative(s)/caregiver(s) (in accordance with local regulation) or observed by the investigator[2]

End point description:

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. An AE could, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

The Safety Set (SS) included all randomized study participants who took at least 1 dose of study medication.

End point type	Primary

End point timeframe:

From the Baseline Period (Day -7) to the End of Study Visit (up to 93 days)

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 outcome. Results were summarized as descriptive statistics only.

End point values	Placebo (SS)	Lacosamide (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	127	128		
Units: percentage of participants				
number (not applicable)	59.1	56.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point title	Absolute change in average daily frequency (ADF) of

	electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point description:

The absolute change in ADF of electrographic partial-onset seizures as measured on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). The analysis consisted of all study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	123	121		
Units: absolute change				
arithmetic mean (standard deviation)	-4.7650 (± 18.0115)	-2.9427 (± 7.4938)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point title	Percent change in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point description:

The percent change in ADF of electrographic partial-onset seizures as measured on the End-of-Maintenance Period video-EEG compared to the End-of-Baseline Period video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). The analysis consisted of all study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	121		
Units: percent change				
arithmetic mean (standard deviation)	-26.7927 (± 58.5564)	-32.3564 (± 65.0255)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved 'seizure-free' status from all seizure types during the End-of-Maintenance (EOM) Period video-EEG

End point title	Percentage of participants who achieved 'seizure-free' status from all seizure types during the End-of-Maintenance (EOM) Period video-EEG

End point description:

A study participant was considered seizure-free from all seizures if the End-of-Maintenance (EOM) Period video-EEG had zero seizures reported from all seizure types (not just partial-onset seizures (POS)).

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). Percentages were based on the number of study participants in the FAS who completed at least 48 hours of interpretable video-EEG recordings during the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

During the End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	117		
Units: percentage of participants				
number (not applicable)	15.8	17.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieved 'seizure-free' status from partial-onset seizure types only during the End-of-Maintenance (EOM) Period video-EEG

End point title	Percentage of participants who achieved 'seizure-free' status from partial-onset seizure types only during the End-of-Maintenance (EOM) Period video-EEG

End point description:

A study participant was considered seizure free from partial-onset seizures (POS) if the End-of-Maintenance (EOM) Period video-EEG had zero POS reported.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). Percentages were based on the number of study participants in the FAS who completed at least 48 hours of interpretable video-EEG recordings during the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

During the End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	117		
Units: percentage of participants				
number (not applicable)	16.7	18.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing a >=25% to <50% reduction in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point title	Percentage of participants experiencing a >=25% to <50% reduction in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point description:

A ≥25% to <50% response was defined as ≥25% to <50% reduction in ADF of electrographic partial-onset seizures (POS) from the End-of-Baseline (EOB) video-EEG to the End-of-Maintenance (EOM) video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). Percentages were based on the number of study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	116		
Units: percentage of participants				
number (not applicable)	18.3	18.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing a 50% to 75% reduction in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point title	Percentage of participants experiencing a 50% to 75% reduction in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point description:

A ≥50% to ≤75% response was defined as ≥50% to ≤75% reduction in ADF of electrographic partial-onset seizures (POS) from the End-of-Baseline (EOB) video-EEG to the End-of-Maintenance (EOM) video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). Percentages were based on the number of study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	116		
Units: percentage of participants				
number (not applicable)	17.5	10.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing a >75% reduction in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point title	Percentage of participants experiencing a >75% reduction in average daily frequency (ADF) of electrographic partial-onset seizures from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point description:

A >75% response was defined as >75% reduction in ADF of electrographic partial-onset seizures (POS) from the End-of-Baseline (EOB) video-EEG to the End-of-Maintenance (EOM) video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). Percentages were based on the number of study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	116		
Units: percentage of participants				
number (not applicable)	20.0	31.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing no change in average daily frequency (ADF) of electrographic partial-onset seizures (between <25% reduction and <25% increase) from EOB Period video-EEG to EOM Period video-EEG

End point title	Percentage of participants experiencing no change in average daily frequency (ADF) of electrographic partial-onset seizures (between <25% reduction and <25% increase) from EOB Period video-EEG to EOM Period video-EEG

End point description:

No change was defined as between <25% reduction and <25% increase in ADF of electrographic partial-onset seizures (POS) from the End-of-Baseline (EOB) video-EEG to the End-of-Maintenance (EOM) video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). Percentages were based on the number of study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	116		
Units: percentage of participants				
number (not applicable)	28.3	27.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing an increase in average daily frequency (ADF) of electrographic partial-onset seizures of >=25% from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point title	Percentage of participants experiencing an increase in average daily frequency (ADF) of electrographic partial-onset seizures of >=25% from End-of-Baseline (EOB) Period video-EEG to End-of-Maintenance (EOM) Period video-EEG

End point description:

An increase was defined as ≥25% increase in ADF of electrographic partial-onset seizures (POS) from the End-of-Baseline (EOB) video-EEG to the End-of-Maintenance (EOM) video-EEG.

Full Analysis Set (FAS) included all study participants in the Safety Set (SS). Percentages were based on the number of study participants in the FAS who had at least 48 hours of interpretable recordings during the EOB Period video-EEG and the EOM Period video-EEG.

End point type	Secondary

End point timeframe:

End-of-Baseline Period (Day -3 to Day 1) to End-of-Maintenance Period (Day 24 to Day 27)

End point values	Placebo (FAS)	Lacosamide (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	116		
Units: percentage of participants				
number (not applicable)	15.0	12.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from the Titration Period (Day 1) to the End of Study Visit (up to 86 days)

Adverse event reporting additional description:

Treatment-emergent AEs (TEAEs) were defined as those events that start on or after the date of first study medication administration and within 30 days following the date of final study medication administration, or whose severity worsens within this time frame.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo (SS)

Reporting group description:

Participants received matching placebo syrup, forming the Safety Set (SS).

Reporting group title	Lacosamide (SS)

Reporting group description:

Participants received lacosamide (LCM) syrup 8 mg/kg/day to 12 mg/kg/day, forming the SS.

Serious adverse events	Placebo (SS)	Lacosamide (SS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 127 (4.72%)	6 / 128 (4.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 127 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 127 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (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			
Oral herpes			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Viral infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 127 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo (SS)	Lacosamide (SS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 127 (23.62%)	31 / 128 (24.22%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	5 / 127 (3.94%)	18 / 128 (14.06%)	
occurrences (all)	6	22	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 127 (11.81%)	7 / 128 (5.47%)	
occurrences (all)	20	9	
Irritability			
subjects affected / exposed	6 / 127 (4.72%)	7 / 128 (5.47%)	
occurrences (all)	6	7	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 127 (10.24%)	6 / 128 (4.69%)	
occurrences (all)	14	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2015	The primary purposes of Protocol Amendment 1 (dated 14 Jan 2015) were to implement the contingent primary efficacy variable for the US, to include sensitivity analyses for the primary endpoint, to clarify the enrollment of study participants <2 years of age, and to provide additional detail regarding the sample size re-estimation at the request of the US Food and Drug Administration (FDA). The following changes were made throughout the protocol: • Contact details for the Clinical Project Manager were updated. • The Sponsor Declaration was updated for electronic signature. • The language of the percentage of study participants <2 years of age to be included in the study was clarified. • The contingent primary efficacy variable for the US was defined. • The anticipated serious adverse event (SAE) table was updated to include a footnote for convulsion. • Text for adherence to the protocol was updated. • Text for healthcare resource use was updated. • A rescue medication assessment was added. • Analysis of the primary efficacy variable for the US and EU was updated. • The sensitivity analysis was described. • Sample size re-estimation text was further detailed.
09 August 2016	The primary purposes of Protocol Amendment 2 (dated 09 Aug 2016) were as follows: • Elements of the study design were clarified, including inclusion and exclusion criteria, withdrawal criteria, permitted and prohibited concomitant medication, and study procedures to make the protocol more patient-friendly and to enhance enrollment. • The protocol was updated per the new UCB protocol template (eg, added text regarding potential drug-induced liver injury [PDILI]).
05 April 2018	The primary purpose of Protocol Amendment 3 (dated 05 Apr 2018) was to address the high variability in video-electroencephalogram (EEG) seizure counts between the site and central reader by removing the central reader. This change was proposed by the FDA as part of a Type C meeting written response obtained on 25 Jan 2018. Additional changes in Protocol Amendment 3 included the following: • Contact information for the clinical trial biostatistician was updated. • The regulatory status of LCM in the US and EU was updated. • The planned number of study participants per age group to reflect UCB's commitment to make every attempt to enroll study participants <2 years of age while recognizing the difficulty of enrolling this age group was clarified. • Ineligibility of an otherwise eligible study participant who had undergone the Baseline EEG due to the narrow visit window for central laboratory measurements was prevented. • It was clarified that "seizure-free" status during the Maintenance Period would be summarized by (1) all seizure types and (2) POS types only. • Hematology and chemistry measurements for the assessment of PDILI events were updated. • The Markov chain Monte Carlo multiple imputation method was replaced with a more appropriate monotone regression method. • An age group was added to the analysis of the primary efficacy variable since randomization was stratified by age group.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported