Clinical trial results:
AN OPEN-LABEL, MULTICENTER, MULTINATIONAL STUDY OF LACOSAMIDE AS FIRST ADD-ON ANTIEPILEPTIC DRUG (AED) TREATMENT IN SUBJECTS WITH PARTIAL-ONSET SEIZURES

Summary

EudraCT number	2009-011181-28
Trial protocol	ES AT FI IT PL NL BG FR GR HU PT DE CZ DK
Global end of trial date	09 August 2013

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	SP0954

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00955357
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES, INC.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, 27617
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	16 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the efficacy and safety of oral LCM as first add-on treatment in subjects with uncontrolled partial-onset seizures with or without secondary generalization after treatment with first adequate AED monotherapy regimen, compared to subjects with uncontrolled partial-onset seizures with or without secondary generalization despite prior adequate treatment with at least 2 AEDs (concurrently or sequentially).

Protection of trial subjects:

None

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	05 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 111
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Mexico: 102
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	United States: 104
Worldwide total number of subjects	456
EEA total number of subjects	233

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	439
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

An estimated 656 subjects were to be enrolled in the study at approximately 130 sites in the US, Europe, and the rest of the world.

Pre-assignment

Screening details:

Overall 461 subjects were enrolled. The Participant Flow refers to the Safety Set (SS) which was defined as all enrolled subjects who took at least 1 dose of Lacosamide. Reasons for discontinuation were only calculated for the SS. 456 subjects were included in the Safety Set.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	First Add-on

Arm description:

Lacosamide added to first adequate monotherapy (no history of AED polytherapy) and epilepsy diagnosis < or = 24 months at Screening.Lacosamide: oral tablet Subjects Titration Phase (6 Weeks): Week 1 - 50 mg tablet Twice daily (bid); Week 2 - 100 mg tablet bid; Week 3 - 150 mg tablet bid;Week 4 - 200 mg tablet bid; Week 5 - 200 mg tablet bid; Week 6 - 150 mg tablet bid OR Week 6 - 200 mg tablet bid Maintenance Phase (24 Weeks): 200 mg tablet bid OR 150 mg tablet bid Taper Phase (1 - 3 Weeks): 50 mg tablet bid for 1 week OR 100 mg tablet bid for 1 week OR 150 mg tablet bid for 1 week

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

Dosage and administration details:

First Add-on: Lacosamide added to first adequate monotherapy (no history of AED polytherapy) and epilepsy diagnosis < or = 24 months at Screening.
Later Add-on: Lacosamide added to 1 to 3 AEDs (with tentatives of at least 2 prior AED treatment regimens) and epilepsy diagnosis > or = 5 years at Screening.

Arm title	Later Add-on

Arm description:

Lacosamide added to 1 to 3 AEDs (with tentatives of at least 2 prior AED treatment regimens) and epilepsy diagnosis > or = 5 years at Screening.Lacosamide: oral tablet Subjects Titration Phase (6 Weeks): Week 1 - 50 mg tablet Twice daily (bid); Week 2 - 100 mg tablet bid; Week 3 - 150 mg tablet bid; Week 4 - 200 mg tablet bid; Week 5 - 200 mg tablet bid;Week 6 - 150 mg tablet bid OR Week 6 - 200 mg tablet bid Maintenance Phase (24 Weeks): 200 mg tablet bid OR 150 mg tablet bid Taper Phase (1 - 3 Weeks): 50 mg tablet bid for 1 week OR 100 mg tablet bid for 1 week OR 150 mg tablet bid for 1 week

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Number of subjects in period 1	First Add-on	Later Add-on
Started	96	360
Completed	68	247
Not completed	28	113
Other (Non compliance to study procedures)	1	-
Patient moving out of area	-	1
Fatal, Serious AE(s)	1	-
Study medication not tolerated	-	1
Non-Fatal, Non-Serious AE(s)	9	62
SAE, non-fatal + AE, non-serious non-fatal	2	1
Consent withdrawn by subject	7	9
Non compliance to study procedures	-	1
Prohibited Antiepileptic Drug change	-	1
Non-Fatal, Serious AE(s)	-	6
Lost to follow-up	3	12
Protocol deviation	5	13
Lack of efficacy	-	6

Baseline characteristics

Reporting groups

Reporting group title	First Add-on

Reporting group description:

Lacosamide added to first adequate monotherapy (no history of AED polytherapy) and epilepsy diagnosis < or = 24 months at Screening.Lacosamide: oral tablet Subjects Titration Phase (6 Weeks): Week 1 - 50 mg tablet Twice daily (bid); Week 2 - 100 mg tablet bid; Week 3 - 150 mg tablet bid;Week 4 - 200 mg tablet bid; Week 5 - 200 mg tablet bid; Week 6 - 150 mg tablet bid OR Week 6 - 200 mg tablet bid Maintenance Phase (24 Weeks): 200 mg tablet bid OR 150 mg tablet bid Taper Phase (1 - 3 Weeks): 50 mg tablet bid for 1 week OR 100 mg tablet bid for 1 week OR 150 mg tablet bid for 1 week

Reporting group title	Later Add-on

Reporting group description:

Lacosamide added to 1 to 3 AEDs (with tentatives of at least 2 prior AED treatment regimens) and epilepsy diagnosis > or = 5 years at Screening.Lacosamide: oral tablet Subjects Titration Phase (6 Weeks): Week 1 - 50 mg tablet Twice daily (bid); Week 2 - 100 mg tablet bid; Week 3 - 150 mg tablet bid; Week 4 - 200 mg tablet bid; Week 5 - 200 mg tablet bid;Week 6 - 150 mg tablet bid OR Week 6 - 200 mg tablet bid Maintenance Phase (24 Weeks): 200 mg tablet bid OR 150 mg tablet bid Taper Phase (1 - 3 Weeks): 50 mg tablet bid for 1 week OR 100 mg tablet bid for 1 week OR 150 mg tablet bid for 1 week

Reporting group values	First Add-on	Later Add-on	Total
Number of subjects	96	360	456
Age Categorical Units: Subjects			
<=18 years	4	7	11
Between 18 and 65 years	82	349	431
>=65 years	10	4	14
Age Continuous Units: years			
median	37.5	38	
full range (min-max)	18 to 82	16 to 74	-
Gender Categorical Units: Subjects			
Female	53	180	233
Male	43	180	223
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	11	6	17
Asian	0	12	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	19	20
White	79	278	357
More than one race	5	45	50
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	24	99	123
Not Hispanic or Latino	72	261	333
Unknown or Not Reported	0	0	0

Weight Units: kilogram median full range (min-max)	 71.8 42 to 132.9	 73 41.9 to 147.4	 -
BMI Units: kilogram per m^2 median full range (min-max)	 25.3 14.5 to 42.5	 25.5 17.3 to 53.9	 -
Height Units: centimeter median full range (min-max)	 166.5 149 to 186	 167.6 140 to 197	 -

End points

End points reporting groups

Reporting group title	First Add-on

Reporting group description:

Lacosamide added to first adequate monotherapy (no history of AED polytherapy) and epilepsy diagnosis < or = 24 months at Screening.Lacosamide: oral tablet Subjects Titration Phase (6 Weeks): Week 1 - 50 mg tablet Twice daily (bid); Week 2 - 100 mg tablet bid; Week 3 - 150 mg tablet bid;Week 4 - 200 mg tablet bid; Week 5 - 200 mg tablet bid; Week 6 - 150 mg tablet bid OR Week 6 - 200 mg tablet bid Maintenance Phase (24 Weeks): 200 mg tablet bid OR 150 mg tablet bid Taper Phase (1 - 3 Weeks): 50 mg tablet bid for 1 week OR 100 mg tablet bid for 1 week OR 150 mg tablet bid for 1 week

Reporting group title	Later Add-on

Reporting group description:

Lacosamide added to 1 to 3 AEDs (with tentatives of at least 2 prior AED treatment regimens) and epilepsy diagnosis > or = 5 years at Screening.Lacosamide: oral tablet Subjects Titration Phase (6 Weeks): Week 1 - 50 mg tablet Twice daily (bid); Week 2 - 100 mg tablet bid; Week 3 - 150 mg tablet bid; Week 4 - 200 mg tablet bid; Week 5 - 200 mg tablet bid;Week 6 - 150 mg tablet bid OR Week 6 - 200 mg tablet bid Maintenance Phase (24 Weeks): 200 mg tablet bid OR 150 mg tablet bid Taper Phase (1 - 3 Weeks): 50 mg tablet bid for 1 week OR 100 mg tablet bid for 1 week OR 150 mg tablet bid for 1 week

Primary: The proportion of subjects who achieved 'seizure-free status' during the first 12 weeks of the Maintenance Phase

End point title	The proportion of subjects who achieved 'seizure-free status' during the first 12 weeks of the Maintenance Phase[1]

End point description:

A subject will be considered seizure-free if the subject completes the first 12 weeks of the Maintenance Phase, reports zero seizures, and has no seizure data missing for any day during the period of time.

This study was intended to assess the efficacy outcomes in the First Add-On Group and the Later Add-On Group individually relative to historical data. Comparisons between the 2 groups should not be attempted and conclusions should not be drawn.

End point type	Primary

End point timeframe:

From Week 7 (end of Week 6) to end of Week 18

Notes:

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

End point values	First Add-on	Later Add-on		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	261		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	37.5	14.9		

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 Screening (Week -1) until the end of the study (up to Week 33).

Adverse event reporting additional description:

Treatment Emergent Adverse Events started on/after the date of first dose and within 30 days of the date of last dose.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Later Add-on

Reporting group description:

Lacosamide added to 1 to 3 AEDs (with tentatives of at least 2 prior AED treatment regimens) and epilepsy diagnosis > or = 5 years at Screening.

Lacosamide: oral tablet

Subjects Titration Phase (6 Weeks):

Week 1 - 50 mg tablet Twice daily (bid);
Week 2 - 100 mg tablet bid;
Week 3 - 150 mg tablet bid;
Week 4 - 200 mg tablet bid;
Week 5 - 200 mg tablet bid;
Week 6 - 150 mg tablet bid
OR
Week 6 - 200 mg tablet bid

Maintenance Phase (24 Weeks):

200 mg tablet bid
OR
150 mg tablet bid

Taper Phase (1 - 3 Weeks):

50 mg tablet bid for 1 week
OR
100 mg tablet bid for 1 week
OR
150 mg tablet bid for 1 week

Reporting group title	First Add-on

Reporting group description:

Lacosamide added to first adequate monotherapy (no history of AED polytherapy) and epilepsy diagnosis < or = 24 months at Screening.

Lacosamide: oral tablet

Subjects Titration Phase (6 Weeks):

Week 1 - 50 mg tablet Twice daily (bid);
Week 2 - 100 mg tablet bid;
Week 3 - 150 mg tablet bid;
Week 4 - 200 mg tablet bid;
Week 5 - 200 mg tablet bid;
Week 6 - 150 mg tablet bid

OR
Week 6 - 200 mg tablet bid

Maintenance Phase (24 Weeks):

200 mg tablet bid
OR
150 mg tablet bid

Taper Phase (1 - 3 Weeks):

50 mg tablet bid for 1 week
OR
100 mg tablet bid for 1 week
OR
150 mg tablet bid for 1 week

Serious adverse events	Later Add-on	First Add-on	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 360 (5.28%)	8 / 96 (8.33%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 360 (0.28%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 360 (0.56%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 360 (0.56%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures			

subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coordination abnormal			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (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 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			

subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (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			
Pyrexia			
subjects affected / exposed	2 / 360 (0.56%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (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	0 / 360 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypochloraemia			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 360 (0.28%)	0 / 96 (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	Later Add-on	First Add-on	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	212 / 360 (58.89%)	53 / 96 (55.21%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	119 / 360 (33.06%)	30 / 96 (31.25%)	
occurrences (all)	159	37	
Somnolence			
subjects affected / exposed	54 / 360 (15.00%)	6 / 96 (6.25%)	
occurrences (all)	65	8	
Headache			

subjects affected / exposed	41 / 360 (11.39%)	13 / 96 (13.54%)	
occurrences (all)	57	19	
Tremor			
subjects affected / exposed	22 / 360 (6.11%)	3 / 96 (3.13%)	
occurrences (all)	23	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	22 / 360 (6.11%)	9 / 96 (9.38%)	
occurrences (all)	22	11	
Eye disorders			
Vision blurred			
subjects affected / exposed	24 / 360 (6.67%)	2 / 96 (2.08%)	
occurrences (all)	28	3	
Diplopia			
subjects affected / exposed	17 / 360 (4.72%)	7 / 96 (7.29%)	
occurrences (all)	17	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	24 / 360 (6.67%)	8 / 96 (8.33%)	
occurrences (all)	27	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 360 (1.11%)	6 / 96 (6.25%)	
occurrences (all)	4	6	
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 360 (1.11%)	5 / 96 (5.21%)	
occurrences (all)	4	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2009	Protocol Amendment 1, dated 06 Oct 2009, provided the following key changes. Based on the date of the amendment, 8 subjects were enrolled globally at the time of the amendment. • The study was conducted only in countries in which LCM was commercially available at the time of study completion; therefore, reference to the fact that LCM was to be provided according to local laws where not commercially available was removed because it was no longer applicable • The liver function test (LFT) withdrawal criteria were revised to reflect the Sponsor's current understanding of the safety profile of LCM based on a comprehensive review of the data from clinical studies • The AEs of special interest were revised to reflect the Sponsor's current understanding of the potential risks of LCM based on a comprehensive review of the data from clinical studies and commitments to regulatory agencies • The approach to detect safety signals was clarified to reflect the Sponsor's current practice • Other changes made in this amendment were minor or administrative
09 July 2010	Protocol Amendment 2, dated 09 Jul 2010, provided the following key changes. Based on the date of the amendment, 111 subjects were enrolled globally at the time of the amendment. • The inclusion criteria were revised to reflect the minimum age of eligible subjects in various countries and regions of the world. In addition, the inclusion criterion for newly diagnosed subjects in the First Add-On Group was updated to clarify that subjects were taking adequate monotherapy and to define what was considered adequate monotherapy for the purpose of this study. The maximum period for the time between the epilepsy diagnosis and the Screening Visit of the First Add-On Group was extended to 24 months in order to better reflect adjunctive therapy in clinical practice • Exclusion criteria were amended to exclude subjects with cranial surgery within the last year prior to the study. Cranial surgery indicated the presence of acute or unstable neurological disorders, which were exclusionary per protocol • Visit windows for titration phone calls were updated to allow for a variation in time of ±1 day relative to Visit 2 • Other changes made in this amendment were minor or administrative
14 December 2010	Protocol Amendment 3, dated 14 Dec 2010, was a substantial amendment and provided the following key changes. Based on the date of the amendment, 242 subjects were enrolled globally at the time of the amendment. • An exclusion criterion was added for known sodium channelopathy. The decision to exclude subjects with known channelopathies, such as Brugada syndrome, from clinical studies with LCM was based on a Food and Drug Administration (FDA) recommendation (17 Aug 2010). The basis for this recommendation was a theoretical concern that enhanced slow inactivation of sodium channels by LCM may have been proarrhythmic in subjects with sodium channelopathies • Revisions were made to withdrawal criteria and follow-up recommendations for abnormal LFTs based on the following: o Newly adopted FDA Guidance for Industry on drug-induced liver injury, which went into effect in Jul 2009, and a recommendation from the FDA to reinsert previously included wording regarding additional withdrawal criteria and follow-up recommendations for abnormal LFTs in LCM protocols o Although no new liver-related safety issues with LCM had been identified, LFT abnormal was added as a postmarketing adverse drug reaction in the LCM Company Core Data Sheet and the EU Summary of Product Characteristics; therefore, LCM protocols were amended to reflect this addition With these revisions, liver-related safety signals continued to be detected via protocol-directed monitoring and additional follow up in ongoing and future LCM clinical studies

11 July 2011	Protocol Amendment 4, dated 11 Jul 2011, was a substantial amendment and provided the following key changes. Based on the date of the amendment, 401 subjects were enrolled globally at the time of the amendment. The changes in Protocol Amendment 4 only affected subjects in the First Add-On Group because the Later Add-On Group's enrollment was closed prior to the amendment's approval in any of the countries. • The Sponsor's name was changed to UCB BIOSCIENCES, INC. Specific Sponsor contact information was updated, and the US phone numbers for reporting serious adverse events (SAEs) were revised. The name and address of the study medication supplier was updated • Switzerland was added as a participating country, with the inclusion criterion being revised to reflect the minimum age of eligible subjects from this country • The inclusion criterion defining the minimum allowed seizure frequency was revised to ≥3 partial-onset seizures (IA, IB, or IC) at any time during the 3 months prior to the Screening Visit from ≥1 partial-onset seizure (IA, IB, or IC) per 28 days. This change did not reflect a change in the number of seizures required in the 3 months prior to Screening, just a change in the frequency per month
11 July 2011	• In addition, the inclusion criterion defining the amount of time that a subject had to be on a stable AED dose regimen and concurrent stable vagus nerve stimulation (VNS) prior to Screening was reduced from 28 days to 7 days to accommodate the First Add-On Group subjects who may have required more frequent AED dose changes in clinical practice than the Later Add-On Group subjects • In accordance with the FDA Draft Guidance for Industry on suicidality (Suicidality: Prospective assessment of occurrence in clinical trials), which went into effect on 29 Oct 2010, the Columbia-Suicide Severity Rating Scale ([C-SSRS] Columbia University Medical Center, 2008) was added to all ongoing and new interventional protocols in order to prospectively assess the occurrence of treatment-emergent suicidality in clinical studies of drug and biological products (FDA, Draft Guidance for Industry 2010) • A list of anticipated SAEs was included in this amendment in compliance with the FDA Guidance for Industry and Investigators on safety reporting requirements for studies conducted under an open Investigational New Drug Application (Safety reporting requirements for IND and BE/BA studies), which went into effect on 28 Mar 2011 (FDA, Guidance for Industry and Investigators, 2010) • Other changes made in this amendment were administrative in nature

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was intended to assess the efficacy outcomes in the First Add-On Group and the Later Add-On Group individually relative to historical data. Comparisons between the 2 groups should not be attempted and conclusions should not be drawn.

Notes: