Clinical trial results:
A multicenter, double-blind, double-dummy, randomized, positive-controlled study comparing the efficacy and safety of Lacosamide (200 to 600 mg/day) to controlled release Carbamazepine (400 to 1200 mg/day), used as monotherapy in subjects (16 years) newly or recently diagnosed with Epilepsy and experiencing partial-onset or generalized tonic-clonic seizures.

Summary

EudraCT number	2010-019765-28
Trial protocol	DE BE CZ FI SE HU ES PT PL SK GB GR IT LV LT BG Outside EU/EEA
Global end of trial date	07 August 2015

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	10 February 2016

Trial information

Trial identification

Sponsor protocol code	SP0993

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01243177
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES GmbH
Sponsor organisation address	Alfred-Nobel-Str. 10, Monheim, Germany, 40789
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000402-PIP02-11
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	17 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to compare the efficacy and safety of Lacosamide (LCM 200 to 600 mg/day) to Carbamazepine controlled release (CBZ-CR 400 to 1200 mg/day) used as monotherapy for at least 1 year, efficacy being measured as a primary endpoint by 6-month seizure freedom, in newly or recently diagnosed epilepsy subjects. The study will employ a noninferiority design to show at least a similar benefit-risk balance for LCM compared with CBZ-CR, using 6-month seizure freedom as primary endpoint.

Protection of trial subjects:

During the study conduct the following measurements were in place in order to protect the trial subjects: ECG measurements, lab including pharmacokinetic (PK) measurements, neurological examinations (complete, brief), HLA-B*1502 allele, HLA-A*3101 allele testing for subjects of Asian ancestry.

Background therapy:

Not applicable

Evidence for comparator:

Carbamazepine is considered an efficacious treatment as monotherapy for partial-onset seizure (POS), is a first choice for treatment for POS and is the most commonly used reference treatment for POS. Carbamazepine-controlled release (CBZ-CR) formulation was used as it minimizes Adverse Events (AEs) and was foreseen to limit the number of discontinuations versus the immediate release formulation of CBZ. In addition, there is precedence for the selection of CBZ-CR as the active comparator in an EU monotherapy registration study (ie, LEV N01061).

Actual start date of recruitment	27 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Bulgaria: 42
Country: Number of subjects enrolled	Czech Republic: 25
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 74

Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 52
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Lithuania: 19
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Portugal: 32
Country: Number of subjects enrolled	Romania: 88
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	Slovakia: 32
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	Sweden: 34
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Ukraine: 34
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	United States: 44
Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	Japan: 20
Country: Number of subjects enrolled	Philippines: 17
Country: Number of subjects enrolled	Korea, Republic of: 47
Country: Number of subjects enrolled	Thailand: 19
Worldwide total number of subjects	886
EEA total number of subjects	586

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)	25
Adults (18-64 years)	742
From 65 to 84 years	116
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study started to enroll in April 2011 and concluded in August 2015.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Analysis Set which is defined as all randomized subjects who took at least 1 dose of study medication and is identical with the Full Analysis Set.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Carer, Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Lacosamide

Arm description: -

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

Dosage and administration details:

• Strengths: 50 mg / 100 mg
• Form: tablets
• Dosage: total daily target dose of 200 mg, 400 mg or 600 mg. 1 dose reduction was allowed from either 600 mg to 500 mg or from 400 mg to 300 mg total daily dose
• Duration: up to 118 weeks

Arm title	Carbamazepine-Controlled Release (CBZ-CR)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Tegretol Retard
Investigational medicinal product code	CBZ-CR
Other name	Carbamazepine controlled release
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Strengths: 200 mg
• Form: tablets
• Dosage: total daily target dose of 400 mg, 800 mg or 1200 mg. 1 dose reduction was allowed from either 1200 mg to 1000 mg or from 800 mg to 600 mg total daily dose
• Duration: up to 118 weeks

Number of subjects in period 1	Lacosamide	Carbamazepine-Controlled Release (CBZ-CR)
Started	444	442
Completed	266	264
Not completed	178	178
AE, serious fatal	-	1
Consent withdrawn by subject	46	38
SAE, fatal + SAE, non-fatal	1	-
AE, non-serious non-fatal	40	58
Other Reason	11	12
Lost to follow-up	15	18
SAE, non-fatal	7	9
Lack of efficacy	47	31
Protocol deviation	11	10
SAE, non-fatal + AE, non-serious non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide
Reporting group description: -	
Reporting group title	Carbamazepine-Controlled Release (CBZ-CR)
Reporting group description: -	

Reporting group values	Lacosamide	Carbamazepine-Controlled Release (CBZ-CR)	Total
Number of subjects	444	442	886
Age Categorical Units: Subjects			
<=18 years	27	19	46
Between 18 and 65 years	355	366	721
>=65 years	62	57	119
Age Continuous Units: years			
arithmetic mean	41.9	41.8	
standard deviation	± 17.9	± 17.2	-
Gender Categorical Units: Subjects			
Male	243	232	475
Female	201	210	411

End points

End points reporting groups

Reporting group title	Lacosamide
Reporting group description: -	
Reporting group title	Carbamazepine-Controlled Release (CBZ-CR)
Reporting group description: -	
Subject analysis set title	Per Protocol Set (Lacosamide treated subjects)
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) was defined as containing all subjects in the Full Analysis Set (FAS) who did not have any important protocol deviations determined to impact the interpretation of primary efficacy.	
Subject analysis set title	Per Protocol Set (CBZ-CR treated subjects)
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) was defined as containing all subjects in the Full Analysis Set (FAS) who did not have any important protocol deviations determined to impact the interpretation of primary efficacy.	

Primary: Proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject

End point title	Proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject
End point description:	
The proportion of subjects remaining seizure free for 6 months (26 weeks) was estimated using Kaplan-Meier methods.	
End point type	Primary
End point timeframe:	
6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject	

End point values	Lacosamide	Carbamazepine-Controlled Release (CBZ-CR)	Per Protocol Set (Lacosamide treated subjects)	Per Protocol Set (CBZ-CR treated subjects)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	444	442	408	397
Units: percentage of subjects				
number (confidence interval 95%)				
percentage of subjects (95 % CI)	89.8 (86.8 to 92.8)	91.1 (88.2 to 94)	91.4 (88.5 to 94.3)	92.8 (90.1 to 95.6)

Statistical analyses

Statistical analysis title	Statistical Analysis (FAS)
Statistical analysis description:	
This was a noninf. assessment of LCM vs CBZ-CR for the proportion of subjects remaining seizure free	

for 6 months at the last evaluated dose. The hypothesis was:
H0: [S(t)LCM] - [S(t)CBZ-CR] <= -12 % vs HA: [S(t)LCM] - [S(t)CBZ-CR] > -12 %, where S(t) (t= 182 days) is the cumulative rate of subjects remaining seizure free for 6 months following stabilization at the last eval. dose (also known as survivorship function), and -12 % represents the noninf. margin based on absolute difference.

Comparison groups	Lacosamide v Carbamazepine-Controlled Release (CBZ-CR)
Number of subjects included in analysis	886
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Mantel Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	2.8

Notes:

[1] - The analysis was stratified based on the number of seizures in the 3 months preceding enrollment (≤2 and >2). The difference in proportion of subjects seizure free on LCM versus CBZ-CR and a corresponding 95 % two-sided confidence interval were produced using Mantel Haenszel methods. The lower limit of the confidence interval was >-12 %, noninferiority of LCM to CBZ-CR was demonstrated. Additionally, the lower confidence limit relative to the CBZ-CR seizure freedom rate was >- 20 %.

Statistical analysis title	Statistical Analysis (PPS)

Statistical analysis description:

This was a noninf. assessment of LCM vs CBZ-CR for the proportion of subjects remaining seizure free for 6 months at the last evaluated dose. The hypothesis was:
H0: [S(t)LCM] - [S(t)CBZ-CR] <= -12 % vs HA: [S(t)LCM] - [S(t)CBZ-CR] > -12 %, where S(t) (t= 182 days) is the cumulative rate of subjects remaining seizure free for 6 months following stabilization at the last eval. dose (also known as survivorship function), and -12 % represents the noninf. margin based on absolute difference.

Comparison groups	Per Protocol Set (Lacosamide treated subjects) v Per Protocol Set (CBZ-CR treated subjects)
Number of subjects included in analysis	805
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	Mantel Haenszel
Parameter estimate	Median difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	2.7

Notes:

[2] - The analysis was stratified based on the number of seizures in the 3 months preceding enrollment (≤2 and >2). The difference in proportion of subjects seizure free on LCM versus CBZ-CR and a corresponding 95 % two-sided confidence interval were produced using Mantel Haenszel methods. The lower limit of the confidence interval was >-12 %, noninferiority of LCM to CBZ-CR was demonstrated. Additionally, the lower confidence limit relative to the CBZ-CR seizure freedom rate was >- 20 %.

Primary: Number of subjects with at least one treatment-emergent Adverse Event (AE) during the Treatment Phase (up to 113 weeks)

End point title	Number of subjects with at least one treatment-emergent Adverse Event (AE) during the Treatment Phase (up to 113 weeks)[3]

End point description:

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Treatment-emergent AEs were defined as AEs that started on or after the date of first dose of study medication and within 30 days following the date of final study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose.

End point type	Primary

End point timeframe:

Duration of the Treatment Phase (up to 113 weeks)

Notes:

[3] - 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 endpoint. Results were summarized using descriptive statistics only.

End point values	Lacosamide	Carbamazepine -Controlled Release (CBZ-CR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	442		
Units: Participants				
Number of subjects	328	332		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who withdraw from the study due to a treatment-emergent Adverse Event (AE) during the Treatment Phase (up to 113 weeks)

End point title	Number of subjects who withdraw from the study due to a treatment-emergent Adverse Event (AE) during the Treatment Phase (up to 113 weeks)[4]

End point description:

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Treatment-emergent AEs were defined as AEs that started on or after the date of first dose of study medication and within 30 days following the date of final study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose.

End point type	Primary

End point timeframe:

Duration of the Treatment Phase (up to 113 weeks)

Notes:

[4] - 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 endpoint. Results were summarized using descriptive statistics only.

End point values	Lacosamide	Carbamazepine -Controlled Release (CBZ-CR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	442		
Units: Participants				
Number of subjects	47	69		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with at least one treatment-emergent Serious Adverse Event (SAE) during the Treatment Phase (up to 113 weeks)

End point title	Number of subjects with at least one treatment-emergent Serious Adverse Event (SAE) during the Treatment Phase (up to 113 weeks)[5]

End point description:

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
A Serious Adverse Event must meet 1 or more predefined criteria like death, life-threatening, etc.
Treatment-emergent AEs were defined as AEs that started on or after the date of first dose of study medication and within 30 days following the date of final study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose.

End point type	Primary

End point timeframe:

Duration of the Treatment Phase (up to 113 weeks)

Notes:

[5] - 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 endpoint. Results were summarized using descriptive statistics only.

End point values	Lacosamide	Carbamazepine -Controlled Release (CBZ-CR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	442		
Units: Participants				
Number of subjects	32	43		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects remaining seizure free for 12 consecutive months (52 consecutive weeks) following stabilization at the last evaluated dose for each

subject

End point title	Proportion of subjects remaining seizure free for 12 consecutive months (52 consecutive weeks) following stabilization at the last evaluated dose for each subject

End point description:

The proportion of subjects remaining seizure free for 12 months (52 weeks) was estimated using Kaplan-Meier methods.

End point type	Secondary

End point timeframe:

12 consecutive months of treatment following stabilization at the last evaluated dose for each subject

End point values	Lacosamide	Carbamazepine -Controlled Release (CBZ-CR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	442		
Units: percentage of subjects				
number (confidence interval 95%)				
percentage of subjects (95 % CI)	77.8 (73.4 to 82.2)	82.7 (78.5 to 86.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected during the whole study from Screening Phase (Week 0) over Evaluation, Maintenance and End of Study Phase up to 121 weeks.

Adverse event reporting additional description:

Adverse Events refer to the Safety Analysis Set consisting of all randomized subjects who took at least 1 dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Carbamazepine-Controlled Release (CBZ-CR)

Reporting group description: -

Reporting group title	Lacosamide

Reporting group description: -

Serious adverse events	Carbamazepine-Controlled Release (CBZ-CR)	Lacosamide	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 442 (10.41%)	36 / 444 (8.11%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaplastic astrocytoma			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 442 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 442 (0.23%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			

subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Smear cervix abnormal			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (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			
Tendon rupture			
subjects affected / exposed	0 / 442 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 442 (0.23%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			

subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 442 (0.23%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			

subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (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	2 / 442 (0.45%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures			
subjects affected / exposed	1 / 442 (0.23%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 442 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 442 (0.23%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor neurone disease			

subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Preictal state			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			
subjects affected / exposed	3 / 442 (0.68%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 442 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	2 / 442 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	2 / 442 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal nerve disorder			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (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			
Antiphospholipid syndrome			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Hernial eventration			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspepsia			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 442 (0.23%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	2 / 442 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress urinary incontinence			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Addison's disease			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (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			
Pneumonia			

subjects affected / exposed	1 / 442 (0.23%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 442 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous pleurisy			

subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 442 (0.23%)	0 / 444 (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	Carbamazepine-Controlled Release (CBZ-CR)	Lacosamide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 442 (40.95%)	165 / 444 (37.16%)	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	35 / 442 (7.92%)	7 / 444 (1.58%)	
occurrences (all)	36	8	
Nervous system disorders			
Headache			
subjects affected / exposed	58 / 442 (13.12%)	60 / 444 (13.51%)	
occurrences (all)	78	82	
Dizziness			
subjects affected / exposed	41 / 442 (9.28%)	53 / 444 (11.94%)	
occurrences (all)	52	61	
Somnolence			
subjects affected / exposed	41 / 442 (9.28%)	27 / 444 (6.08%)	
occurrences (all)	47	28	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	49 / 442 (11.09%)	34 / 444 (7.66%)	
occurrences (all)	55	38	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed occurrences (all)	23 / 442 (5.20%) 30	26 / 444 (5.86%) 32	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	29 / 442 (6.56%) 37	29 / 444 (6.53%) 42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2010	Global Protocol Amendment 1 dated 13 Dec 2010 provided the following primary and other key revisions. No subjects were randomized prior to the date of this amendment. The primary purpose of this substantial protocol amendment was to add an exclusion criterion for known sodium channelopathy and revise withdrawal criteria and follow-up recommendations for abnormal liver function tests (LFTs). The rationales for these changes are described below. The decision to exclude subjects with known channelopathies, such as Brugada syndrome, from clinical studies with Lacosamide (LCM) was based on a recommendation from the US FDA (17 Aug 2010). The basis for this request was a theoretical concern that enhanced slow inactivation of sodium channels by LCM may be proarrhythmic in subjects with sodium channelopathies. The decision to re-insert additional withdrawal criteria and follow-up recommendations for abnormal LFTs was based on the following: 1. Newly adopted FDA Guidance on Drug-Induced Liver Injury (July 2009) and a recommendation from the US FDA to re-insert previously included wording regarding additional withdrawal criteria and follow-up recommendations for abnormal LFTs in LCM protocols. 2. Although no new liver-related safety issues with LCM have been identified, LFT abnormal has been added as a postmarketing adverse drug reaction in the LCM Company Core Data Sheet (CCDS) and the EU Summary of Product Characteristics (SmPC). Therefore, LCM protocols are being 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.
13 December 2010	Other key revisions included the following: - Clarification that minors were included in some countries if legally permitted - Addition of language with regard to male contraception - Clarification of the guidance followed in the analysis of the primary efficacy variable - Change of the Screening Phase from 7 days ±2 days to 7 days ±5 days - Removal of the desmethyl metabolite of LCM from bioanalytical analysis - Clarification that the fasting period prior to blood sample collection for additional laboratory tests (fasting serum lipid levels and thyroid and sex hormone concentrations) should be 8 hours - Further clarification for the sites The remainder of the changes in this amendment were minor or administrative in nature.
18 November 2011	Global Protocol Amendment 2, dated 18 Nov 2011 provided the following key revisions. A total of 61 subjects (32 subjects and 29 subjects in the LCM and CBZ-CR treatment groups, respectively) were randomized prior to the date of this amendment. The primary purposes of this substantial protocol amendment were to revise the exclusion criteria related to a history of suicidality and to add withdrawal criteria related to suicidality. The rationale for these changes is described below. As required by the US FDA, the Columbia-Suicide Severity Rating Scale (C-SSRS) was added to evaluate and identify subjects at risk for suicide while participating in a clinical study of a drug with central nervous system (CNS) activity (FDA, Guidance for Industry, 2010). The sponsor's name was also changed to UCB BIOSCIENCES GmbH, and specific Sponsor contact information was updated. The remainder of the changes in this amendment were minor or administrative in nature.

01 August 2012	Global Protocol Amendment 3, dated 01 Aug 2012 provided the following key revisions. A total of 206 subjects (103 subjects and 103 subjects in the LCM and CBZ-CR treatment groups, respectively) were randomized prior to the date of this amendment. The primary purpose of this substantial protocol amendment was to provide clarification for the efficacy variables, withdrawal criteria (eg, following a seizure that occurred after dose reduction), and the use of concomitant medications that may have interacted with study medication. The remainder of the changes in this amendment were minor or administrative in nature.
27 November 2012	Global Protocol Amendment 4, dated 27 Nov 2012 provided the following key revisions. A total of 313 subjects (156 subjects and 157 subjects in the LCM and CBZ-CR treatment groups, respectively) were randomized prior to the date of this amendment. With the expansion of SP0993 to investigational sites in the US, and based on a request from the US FDA, a primary purpose of this substantial protocol amendment was to include language that reflected the FDA's requirements. Exclusion criterion 11 (regarding prior treatment of epilepsy with any antiepileptic drug (AED)) was modified to indicate that acute and subacute seizure treatment was accepted with a maximum of 2 weeks duration and if treatment was stopped "at least 3 days prior to randomization" formerly "at least 1 week before Visit 1"). This change decreased the duration of time during which subjects could potentially go untreated before initiating study medication in SP0993, therefore increasing subject safety. Most withdrawal seizures were expected to occur within 72 hours of AED withdrawal, and most AEDs (including benzodiazepines) were expected to be cleared within this time period with little potential for drug interactions. A withdrawal criterion was clarified for situations in which a subject experienced a seizure during the Evaluation Phase at the maximum dosage of study medication. Section 7.8.3.4 of the protocol (Permitted agents whose plasma levels may be affected by CBZ) was updated with the addition of alprazolam and the deletion of amitriptyline (amitriptyline use as an antidepressant is disallowed in Section 7.8.2 of the Protocol). The remainder of the changes in this amendment were minor or administrative in nature.
14 March 2013	Global Protocol Amendment 5, dated 14 Mar 2013 provided the following key revisions. This amendment was submitted only to local ethic committees in Spain and was not implemented by any site, therefore, no subjects were randomized under this amendment. Human leukocyte antigen (HLA)-A*3101 is associated with an increased risk of CBZ-induced cutaneous adverse drug reactions in people of European descent and the Japanese. Although there are insufficient data supporting a recommendation for HLA-A*3101 screening before starting CBZ treatment (Tegretol Prolonged Release 200mg, SmPC of Carbamazepine-United Kingdom; Drug Safety Update Dec 2012, vol 6, issue 5: A1), the protocol was updated based on a recommendation from the Japanese regulatory authorities (Pharmaceuticals and Medical Devices Agency [PMDA]) to exclude subjects of Asian ancestry who tested positive for the HLA-A*3101 allele. This was in addition to the exclusion of subjects of Asian ancestry who tested positive for the HLA-B*1502 allele. Screening of subjects of Asian ancestry for the HLA-A*3101 allele was previously included in a country-specific protocol amendment (Protocol Amendment 4.2 [Japan]) and was then incorporated with the global Protocol Amendment 5.

14 March 2013	Contraceptive measures for male participants (exclusion criterion 30) were deleted because preclinical studies did not find any LCM-related findings at any dose level on male reproductive function. Lacosamide did not show any effects on reproductive function in male rats and no abnormalities in the F1 offspring of male rats were observed in peri-postnatal study. Female contraception requirements (exclusion criterion 27) were adjusted based on World Health Organization (WHO) guidance on highly effective methods of contraception for women of childbearing potential taking enzyme-inducing AEDs (WHO, 2010). In Section 7.8.2 of the protocol (Concomitant non-AED treatments), text regarding antidepressant and neuroleptic use was modified to permit the introduction of antidepressants (eg, serotonin-selective reuptake inhibitors [SSRIs]) that do not cause drug interaction issues and do not interfere with epilepsy therapy. In Section 7.8.3.4 of the protocol (Permitted agents whose plasma levels may be affected by CBZ), alprazolam was removed as a permitted medication. This change was made in order to be consistent with other sections of the protocol that limit the use of benzodiazepines. The remainder of the changes in this amendment were minor or administrative in nature.
20 May 2013	Global Protocol Amendment 6 dated 20 May 2013 included all of the changes in Protocol Amendment 5 and also provided the following key revisions. A total of 476 subjects (239 subjects and 237 subjects in the LCM and CBZ-CR treatment groups, respectively) were randomized prior to the date of this amendment. In Section 7.8.2 of the protocol (Concomitant non-AED treatments), the following sentence was deleted in this amendment: “Oral contraceptive use is allowed if ethinylestradiol dosage is at least 50 µg per intake.” This correction was made to be consistent with exclusion criterion 27 that no longer required a minimum dosage of ethinylestradiol (modification in global Protocol Amendment 5).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported