Clinical trial results:
A multicenter, double-blind, double-dummy, follow-up study evaluating the long-term safety of lacosamide (200 to 600mg/day) in comparison with carbamazepine (400 to 1200mg/day), used as monotherapy in subjects with partial-onset or generalized tonic-clonic seizures >= 16 years of age coming from the SP0993 study.

Summary

EudraCT number	2010-021238-74
Trial protocol	DE HU ES BE SE FI PT GB CZ SK PL IT LV LT GR BG Outside EU/EEA
Global end of trial date	03 January 2017

Results information	
Result version number	v1 (current)
This version publication date	13 July 2017
First version publication date	13 July 2017

Trial information

Trial identification	
Sponsor protocol code	SP0994

Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01465997
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	UCB BIOSCIENCES GmbH
Sponsor organisation address	Alfred-Nobel-Strasse 10, Monheim, Germany, 40789
Public contact	Clinical Trial Registries and 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	04 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To obtain information about the long-term safety of Lacosamide (LCM) in comparison with Carbamazepine (CBZ-CR) when used as monotherapy in subjects with recently diagnosed partial-onset or generalized tonic-clonic seizures. To allow subjects who completed the monotherapy study SP0993 to continue to receive LCM or CBZ-CR.

Protection of trial subjects:

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

Background therapy:

Adjunctive chronic treatment with antiepileptic drugs (AEDs) was not allowed. Other background therapy was permitted, as defined in the study protocol.

Evidence for comparator:

In the 2006 and 2013 International League Against Epilepsy (ILAE) treatment guidelines, carbamazepine (CBZ-CR) is considered an efficacious treatment as monotherapy for partial-onset-seizures (POS) and is a first choice for treatment for POS. Carbamazepine (controlled release) is preferred as it minimizes AEs and limits the number of discontinuations. For these reasons, CBZ-CR may be regarded as the best standard comparator.

Actual start date of recruitment	16 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Bulgaria: 28
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Latvia: 2

Country: Number of subjects enrolled	Lithuania: 15
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Philippines: 16
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Romania: 58
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Slovakia: 19
Country: Number of subjects enrolled	Korea, Republic of: 32
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Sweden: 23
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Ukraine: 16
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	548
EEA total number of subjects	366

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)	7
Adults (18-64 years)	464
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment started in May 2012 and concluded in January 2017 - 551 patients.
Due to the political and civil unrest in Luhansk PAREXEL was not able to conduct further site visits to one site in Ukraine and to collect further data for 2 subjects,they were excluded from SP0994, leaving 549 patients in the Enrolled Set out of 551 initially enrolled.

Pre-assignment

Screening details:

A total of 549 subjects gave informed consent in SP0994 and were included in the Enrolled Set, 548 subjects received at least 1 dose of study medication and were included in the Safety Set (SS). Participant Flow refers to the Safety Population including all enrolled subjects who received at least 1 dose of study medication in the current study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lacosamide

Arm description:

50 and 100 mg tablets of Lacosamide given as 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day or 600 mg/day throughout the Treatment Period (Maximum 3.5 Years). CBZ-CR placebo capsules were administered to maintain the blinding.

Arm type	Experimental
Investigational medicinal product name	Carbamazepine-Controlled Release-placebo
Investigational medicinal product code	CBZ-CR-PBO
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to LCM treatment received CBZ-CR-PBO capsules to maintain the blinding.

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

Dosage and administration details:

LCM was orally administered twice daily (bid) in 2 equally divided doses of 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day or 600 mg/day throughout the Treatment Period (Maximum 3.5 Years).

Arm title	Carbamazepine-Controlled Release (CBZ-CR)

Arm description:

200 mg tablets of Carbamazepine-CR given as 400 mg/day, 600 mg/day, 800 mg/day, 1000 mg/day or 1200 mg/day throughout the Treatment Period (Maximum of 3.5 Years). Lacosamide placebo capsules were administered to maintain the blinding.

Arm type	Active comparator

Investigational medicinal product name	Lacosamide-placebo
Investigational medicinal product code	LCM-PBO
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects randomized to CBZ-CR treatment received LCM-PBO tablets to maintain the blinding.

Investigational medicinal product name	Carbamazepine-Controlled Release
Investigational medicinal product code	CBZ-CR
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

CBZ-CR was orally administered twice daily (bid) in 2 equally divided doses of 400 mg/day, 500 mg/day or 600 mg/day throughout the Treatment Period (Maximum 3.5 Years).

Number of subjects in period 1	Lacosamide	Carbamazepine-Controlled Release (CBZ-CR)
Started	279	269
Completed	211	180
Not completed	68	89
Adverse event, serious fatal	-	1
investigator's decision	1	1
decision by site staff	-	1
withdrew before follow-up	-	13
Consent withdrawn by subject	32	35
local lab unblinded site	1	-
Adverse event, non-fatal	12	22
subject left participation SP0993	-	1
subject withdrew consent	1	-
Lost to follow-up	6	9
sponsor's decision	1	1
Lack of efficacy	13	1
Protocol deviation	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Lacosamide

50 and 100 mg tablets of Lacosamide given as 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day or 600 mg/day throughout the Treatment Period (Maximum 3.5 Years). CBZ-CR placebo capsules were

End points

End points reporting groups

Reporting group title	Lacosamide
Reporting group description:	
50 and 100 mg tablets of Lacosamide given as 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day or 600 mg/day throughout the Treatment Period (Maximum 3.5 Years). CBZ-CR placebo capsules were administered to maintain the blinding.	
Reporting group title	Carbamazepine-Controlled Release (CBZ-CR)
Reporting group description:	
200 mg tablets of Carbamazepine-CR given as 400 mg/day, 600 mg/day, 800 mg/day, 1000 mg/day or 1200 mg/day throughout the Treatment Period (Maximum of 3.5 Years). Lacosamide placebo capsules were administered to maintain the blinding.	
Subject analysis set title	Lacosamide (SS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
50 and 100 mg tablets of Lacosamide given as 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day or 600 mg/day throughout the Treatment Period (Maximum 3.5 Years). CBZ-CR placebo capsules were administered to maintain the blinding.	
Subject analysis set title	Carbamazepine-Controlled Release (CBZ-CR) (SS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
200 mg tablets of Carbamazepine-CR given as 400 mg/day, 600 mg/day, 800 mg/day, 1000 mg/day or 1200 mg/day throughout the Treatment Period (Maximum of 3.5 Years). Lacosamide placebo capsules were administered to maintain the blinding.	

Primary: Number of subjects with at least one treatment-emergent Adverse Event (AE) during the Treatment Phase (Maximum of 3.5 Years)

End point title	Number of subjects with at least one treatment-emergent Adverse Event (AE) during the Treatment Phase (Maximum of 3.5 Years)[1]
End point description:	
Treatment-emergent AEs were defined as those events which started on or after the date of first dose of SP0994 study medication, or events in which severity worsened on or after the date of first dose of SP0994 study medication. AEs which occurred within 30 days after last dose of study medication were considered treatment emergent.	
End point type	Primary
End point timeframe:	
Up to 3.5 Years (Duration of the Treatment Phase)	

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 end point. Results were summarized as descriptive statistics only.

End point values	Lacosamide (SS)	Carbamazepine-Controlled Release (CBZ-CR) (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	279	269		
Units: Participants				
Number of subjects	181	182		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who withdrew from the study due to a treatment-emergent Adverse Event (AE) during the Treatment Phase (Maximum 3.5 Years)

End point title	Number of subjects who withdrew from the study due to a treatment-emergent Adverse Event (AE) during the Treatment Phase (Maximum 3.5 Years)[2]

End point description:

Treatment-emergent AEs were defined as those events which started on or after the date of first dose of SP0994 study medication, or events in which severity worsened on or after the date of first dose of SP0994 study medication. AEs which occurred within 30 days after last dose of study medication were considered treatment emergent.

End point type	Primary

End point timeframe:

Up to 3.5 Years (Duration of the Treatment Phase)

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 end point. Results were summarized as descriptive statistics only.

End point values	Lacosamide	Carbamazepine -Controlled Release (CBZ-CR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	279	269		
Units: Patricipants				
Number of subjects	12	21		

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 (Maximum of 3.5 years)

End point title	Number of subjects with at least one treatment-emergent Serious Adverse Event (SAE) during the Treatment Phase (Maximum of 3.5 years)[3]

End point description:

A Serious Adverse Event is any untoward medical occurrence that at any dose results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity is a congenital anomaly/birth defect.

End point type	Primary

End point timeframe:

Up to 3.5 Years (Duration of the Treatment Phase)

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 end point. Results were summarized as descriptive statistics only.

End point values	Lacosamide	Carbamazepine -Controlled Release (CBZ-CR)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	279	269		
Units: Participants				
Number of subjects	32	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the entire study period, up to 5 years	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Lacosamide (SS)
Reporting group description:	
50 and 100 mg tablets of Lacosamide given as 200 mg/day, 300 mg/day, 400 mg/day, 500 mg/day or 600 mg/day throughout the Treatment Period (Maximum 3.5 Years). CBZ-CR placebo capsules were administered to maintain the blinding.	
Reporting group title	Carbamazepine-Controlled Release (CBZ-CR) (SS)
Reporting group description:	
200 mg tablets of Carbamazepine-CR given as 400 mg/day, 600 mg/day, 800 mg/day, 1000 mg/day or 1200 mg/day throughout the Treatment Period (Maximum of 3.5 Years). Lacosamide placebo capsules were administered to maintain the blinding.	

Serious adverse events	Lacosamide (SS)	Carbamazepine-Controlled Release (CBZ-CR) (SS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 279 (11.47%)	22 / 269 (8.18%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myelodysplastic syndrome			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign breast neoplasm			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy on contraceptive			
subjects affected / exposed	0 / 279 (0.00%)	2 / 269 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Epididymitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 279 (0.36%)	2 / 269 (0.74%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (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 / 279 (0.00%)	2 / 269 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (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			

Laceration			
subjects affected / exposed	1 / 279 (0.36%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (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 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
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 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			

subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haematoma			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
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 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 279 (0.72%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 279 (0.36%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	2 / 279 (0.72%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (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 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White matter lesion			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible ischaemic neurological deficit			

subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
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 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular ataxia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Exophthalmos			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Lumbar hernia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			

subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder disorder			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 279 (0.36%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint instability			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 279 (0.36%)	0 / 269 (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	0 / 279 (0.00%)	3 / 269 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 279 (0.00%)	1 / 269 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2011	The primary purpose of this substantial protocol amendment was to revise the withdrawal criteria and follow-up recommendations for abnormal liver function tests (LFTs) based upon newly adopted US 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. In addition, clarification of study procedures for the sites was included.
09 December 2011	The primary purposes of this substantial protocol amendment were to revise the exclusion criterion related to a history of suicidality, add a withdrawal criterion related to suicidality, and add a list of anticipated serious adverse events (SAEs). The Columbia-Suicide Severity Rating Scale (C-SSRS; Columbia University Medical Center, 2008) was implemented to evaluate and identify subjects at risk for suicide while participating in a clinical study of a drug with central nervous system activity based upon the US FDA's recommendation (FDA, Guidance for Industry, 2010). In addition, a withdrawal criterion related to suicidality and a list of anticipated SAEs, in compliance with the recent US FDA guidance on safety reporting requirements for studies conducted under an open Investigational New Drug (effective 28 Mar 2011; FDA, Guidance for Industry and Investigators, 2010) were added. The Sponsor's name was changed to UCB BIOSCIENCES GmbH and specific sponsor contact information was updated. In addition, details for the SP0994 Open-Label Phase were provided.
22 August 2013	Based on the date of the amendment, 116 subjects entered the study prior to the date of this amendment. The primary purpose of this substantial protocol amendment was to eliminate the Open-Label Phase of the study, including associated Open-Label Visits. SP0994 was blinded until SP0993 database lock and unblinding. Following the database lock and unblinding of SP0993, SP0994 was unblinded and closed for all subjects. Subjects in SP0994 who were receiving LCM had access to open-label follow-up treatment with LCM according to local laws. Subjects who were receiving CBZ-CR and wished to continue treatment after the close of SP0994 may have received prescribed CBZ (ie, not supplied by UCB BIOSCIENCES). For clarification, the exploratory efficacy variable "retention rate (ie, duration of treatment in the study)," was changed to "time to discontinuation." Section 7.8 of the protocol (concomitant medications/treatments) was updated to be consistent with the corresponding section of the SP0993 protocol.
27 February 2015	Based on the date of the amendment, 478 subjects entered the study prior to the date of this amendment. The primary purpose of this substantial protocol amendment was to add additional routine visits to SP0994 in case the study was still ongoing and the subject had passed Visit 14.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported