Clinical trial results:
A Multi-Center, open-label, randomized study to evaluate the long term effectiveness of Levetiracetam as monotherapy in comparison with Oxcarbazepine in subjects with newly or recently diagnosed partial epilepsy

Summary

EudraCT number	2014-002713-32
Trial protocol	Outside EU/EEA
Global end of trial date	15 July 2014

Results information

Result version number	v2 (current)
This version publication date	30 January 2016
First version publication date	11 July 2015
Version creation reason	• Correction of full data set Revision of full data set results to be consistent with results posted on Clinicaltrials.gov.

Trial information

Trial identification

Sponsor protocol code	N01367

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01498822
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Korea UCB Co., Ltd.
Sponsor organisation address	127 Teheran-ro, Seoul, Korea, Republic of, 135-911
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)	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	09 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long term effectiveness of Levetiracetam (LEV) monotherapy on Treatment Failure Rate in subjects with newly diagnosed partial onset seizures with or without secondary generalized seizure, compared to Oxcarbazepine (OXC) monotherapy over 50 weeks from the first dose of study medication and to demonstrate that monotherapy with LEV (1,000 to 3,000 mg/day) is non-inferior to monotherapy with OXC (900 to 2,400 mg/day).

Protection of trial subjects:

Subjects were informed of potential risks and discomforts from the study medications and the study procedures, and the fact that they would receive the most appropriate treatment when they suffer injuries and inform the doctor and that the doctors would make every efforts to minimize any discomforts from the study procedure, for example: needle stick, bruising at the blood sample site, reaction to the ECG patch adhesive, number of visits.

Background therapy:

Not applicable

Evidence for comparator:

For subjects with newly diagnosed or yet untreated epilepsy, the question still remains regarding the best choice of AED(s) with the best evidence for long term efficacy and safety as initial monotherapy. Apart from a well designed, randomized controlled trial for registration purpose, which demonstrated the non-inferiority of LEV compared to CBZ-CR in newly-diagnosed patients with partial epilepsy, KOMET study suggested broad-spectrum efficacy of LEV with tolerability similar to that of VPA-ER and CBZ-CR, and SANAD study suggested that further AED needs to be compared with LTG or possibly OXC rather than CBZ in partial onset seizures for monotherapy.
In order to provide neurologists with the best evidence in selecting efficacious and tolerable long-term treatments among commonly prescribed newer AEDs, a comparison including LEV and OXC is warranted. Comparing LEV to OXC may provide evidence to support LEV use for subjects with newly diagnosed partial epilepsy, and provide reliable data for clinical practice that takes patient preference into account.

Actual start date of recruitment	08 June 2011
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	Korea, Republic of: 353
Worldwide total number of subjects	353
EEA total number of subjects	0

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)	14
Adults (18-64 years)	301
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in June 2011. A total of 27 investigators enrolled 353 subjects at 23 sites in Korea.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set, consisting of all subjects who were randomized in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Levetiracetam

Arm description:

Levetiracetam twice a day treatment Group
250 mg and 500 mg Levetiracetam tablet, 1000 mg-3000 mg/day, maximum 50 weeks including initial up titration of 500 mg/day for 2 weeks

Arm type	Experimental
Investigational medicinal product name	Levetiracetam
Investigational medicinal product code	LEV
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg and 500 mg Levetiracetam tablet, 1000 mg-3000 mg/day, maximum 50 weeks including initial up titration of 500 mg/day for 2 weeks

Arm title	Oxcarbazepine

Arm description:

Oxcarbazepine twice a day treatment Group
150 mg and 300 mg Oxcarbazepine tablet, 900 mg-2400 mg/day, maximum 50 weeks including 2 weeks of up titration (300 mg/day 1 week then 600 mg/day 1 week)

Arm type	Active comparator
Investigational medicinal product name	Oxcarbazepine
Investigational medicinal product code	OXC
Other name	Trileptal
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg and 300 mg Oxcarbazepine tablet, 900 mg-2400 mg/day, maximum 50 weeks including 2 weeks of up titration (300 mg/day 1 week then 600 mg/day 1 week)

Number of subjects in period 1	Levetiracetam	Oxcarbazepine
Started	175	178
Completed	121	122
Not completed	54	56
Adverse event, serious fatal	1	1
Consent withdrawn by subject	15	25
Other Reason	5	2
AE, non-serious non-fatal	8	17
Lost to follow-up	8	3
SAE, non-fatal	2	2
Lack of efficacy	7	2
Protocol deviation	8	4

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam
Reporting group description:	
Levetiracetam twice a day treatment Group 250 mg and 500 mg Levetiracetam tablet, 1000 mg-3000 mg/day, maximum 50 weeks including initial up titration of 500 mg/day for 2 weeks	
Reporting group title	Oxcarbazepine
Reporting group description:	
Oxcarbazepine twice a day treatment Group 150 mg and 300 mg Oxcarbazepine tablet, 900 mg-2400 mg/day, maximum 50 weeks including 2 weeks of up titration (300 mg/day 1 week then 600 mg/day 1 week)	

Reporting group values	Levetiracetam	Oxcarbazepine	Total
Number of subjects	175	178	353
Age categorical Units: Subjects			
<=18 years	14	13	27
Between 18 and 65 years	145	143	288
>=65 years	16	22	38
Age Continuous Units: years			
arithmetic mean	39.5	42.7	
standard deviation	± 16.7	± 17.3	-
Gender categorical Units: Subjects			
Female	84	79	163
Male	91	99	190
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	174	178	352
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	1	0	1
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Levetiracetam
Reporting group description:	
Levetiracetam twice a day treatment Group 250 mg and 500 mg Levetiracetam tablet, 1000 mg-3000 mg/day, maximum 50 weeks including initial up titration of 500 mg/day for 2 weeks	
Reporting group title	Oxcarbazepine
Reporting group description:	
Oxcarbazepine twice a day treatment Group 150 mg and 300 mg Oxcarbazepine tablet, 900 mg-2400 mg/day, maximum 50 weeks including 2 weeks of up titration (300 mg/day 1 week then 600 mg/day 1 week)	
Subject analysis set title	Per Protocol Set (OXC treated subjects)
Subject analysis set type	Per protocol
Subject analysis set description:	
150 mg and 300 mg Oxcarbazepine tablet, 900 mg-2400 mg/day, maximum 50 weeks including 2 weeks of up titration (300 mg/day 1 week then 600 mg/day 1 week)	
Subject analysis set title	Per Protocol Set (LEV treated subjects)
Subject analysis set type	Per protocol
Subject analysis set description:	
250 mg and 500 mg Levetiracetam tablet, 1000 mg-3000 mg/day, maximum 50 weeks including initial up titration of 500 mg/day for 2 weeks	
Subject analysis set title	Full Analysis Set (OXC treated subjects)
Subject analysis set type	Full analysis
Subject analysis set description:	
150 mg and 300 mg Oxcarbazepine tablet, 900 mg-2400 mg/day, maximum 50 weeks including 2 weeks of up titration (300 mg/day 1 week then 600 mg/day 1 week)	
Subject analysis set title	Full Analysis Set (LEV treated subjects)
Subject analysis set type	Full analysis
Subject analysis set description:	
250 mg and 500 mg Levetiracetam tablet, 1000 mg-3000 mg/day, maximum 50 weeks including initial up titration of 500 mg/day for 2 weeks	

Primary: Percentage of subjects with a treatment failure

End point title	Percentage of subjects with a treatment failure
End point description:	
Treatment failure is defined as (1) Dropout due to related intolerable adverse event, lack of efficacy or need for addition of another Antiepileptic Drug (AED), or (2) need of a 1-step down-titration, within 50 weeks from the first dose of study medication.	
End point type	Primary
End point timeframe:	
Week 0 (First Dose) to Week 50	

End point values	Per Protocol Set (OXC treated subjects)	Per Protocol Set (LEV treated subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	128	118		
Units: percentage of subjects				

number (not applicable)				
percentage of subjects	23.4	12.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Per Protocol Set (LEV treated subjects) v Per Protocol Set (OXC treated subjects)
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Wald methodology
Parameter estimate	Absolut difference
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.2
upper limit	-1.2

Notes:

[1] - The primary analysis of this study aimed to demonstrate that LEV was noninferior to OXC with respect to the treatment failure rate in the Per Protocol Set. The noninferiority margin was 15 %.

Secondary: Time to the first seizure defined as the time from the first dose of medication to the occurrence of the first seizure during the 48 weeks Treatment Period

End point title	Time to the first seizure defined as the time from the first dose of medication to the occurrence of the first seizure during the 48 weeks Treatment Period

End point description:

Dispersion measures for the statistic were not part of the analysis (or it's specification).
Kaplan-Meier estimation of percentage of event-free subjects does not fall to or below 50 %, therefore no median time to event could be estimated for the OXC Group.

End point type	Secondary

End point timeframe:

From Week 2 to Week 50 (During Treatment Period)

End point values	Full Analysis Set (OXC treated subjects)	Full Analysis Set (LEV treated subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	171[2]	173[3]		
Units: months				
median (full range (min-max))				
Median (Full Range)	99 (-999 to 999)	7.556 (-999 to 999)		

Notes:

[2] - -999/99/999 = not estimable

[3] - -999/999 = Dispersion measures not part of the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who achieved seizure freedom for 24 consecutive weeks during the 48 weeks Treatment Period at any time

End point title	Percentage of subjects who achieved seizure freedom for 24 consecutive weeks during the 48 weeks Treatment Period at any time

End point description:

24-week Seizure Freedom (rate) defined as the number and percentage of subjects who achieved seizure freedom for 24 consecutive weeks during the Treatment Period at any time

End point type	Secondary

End point timeframe:

From Week 2 to Week 50 (During Treatment Period)

End point values	Full Analysis Set (OXC treated subjects)	Full Analysis Set (LEV treated subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	171	173		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	58.5	53.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who achieved seizure freedom during the 48 weeks Treatment Period

End point title	Percentage of subjects who achieved seizure freedom during the 48 weeks Treatment Period

End point description:

48-week Seizure Freedom (rate) defined as the number and percentage of subjects who achieved seizure freedom during the Treatment Period

End point type	Secondary

End point timeframe:

From Week 2 to Week 50 (During Treatment Period)

End point values	Full Analysis Set (OXC treated subjects)	Full Analysis Set (LEV treated subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	171	173		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	40.9	34.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected up to 57 Weeks from Visit 1 (Week -1) to the end of the post-treatment period (down-titration visit, safety follow-up visit).

Adverse event reporting additional description:

Adverse Events refer to the Safety Set (SS). SS consisted of all subjects who were randomized and received at least 1 (partial) dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Oxcarbazepine

Reporting group description:

Oxcarbazepine twice a day treatment Group

150 mg and 300 mg Oxcarbazepine tablet, 900 mg-2400 mg/day, maximum 50 weeks including 2 weeks of up titration (300 mg/day 1 week then 600 mg/day 1 week)

Reporting group title	Levetiracetam

Reporting group description:

Levetiracetam twice a day treatment Group

250 mg and 500 mg Levetiracetam tablet, 1000 mg-3000 mg/day, maximum 50 weeks including initial up titration of 500 mg/day for 2 weeks

Serious adverse events	Oxcarbazepine	Levetiracetam	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 174 (8.62%)	15 / 173 (8.67%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	2 / 174 (1.15%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 174 (0.57%)	1 / 173 (0.58%)	
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	5 / 174 (2.87%)	4 / 173 (2.31%)	
occurrences causally related to treatment / all	0 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 174 (0.57%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Encephalopathy			
subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
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			
Upper airway obstruction			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (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			
Flank pain			
subjects affected / exposed	0 / 174 (0.00%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 174 (0.57%)	1 / 173 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 173 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Oxcarbazepine	Levetiracetam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 174 (53.45%)	67 / 173 (38.73%)	
Nervous system disorders			
Headache			

subjects affected / exposed	36 / 174 (20.69%)	25 / 173 (14.45%)	
occurrences (all)	53	29	
Dizziness			
subjects affected / exposed	50 / 174 (28.74%)	25 / 173 (14.45%)	
occurrences (all)	70	30	
Somnolence			
subjects affected / exposed	24 / 174 (13.79%)	22 / 173 (12.72%)	
occurrences (all)	30	30	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	13 / 174 (7.47%)	3 / 173 (1.73%)	
occurrences (all)	16	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 174 (10.92%)	14 / 173 (8.09%)	
occurrences (all)	21	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported