Clinical trial results:
A multicenter, open-label, randomized, parallel-group, active-controlled study comparing the efficacy and safety of Levetiracetam to Carbamazepine used as monotherapy in subjects (16 years) newly or recently diagnosed as suffering from epilepsy and experiencing partial seizures

Summary

EudraCT number	2015-004586-84
Trial protocol	Outside EU/EEA
Global end of trial date	30 September 2015

Results information

Result version number	v1 (current)
This version publication date	03 April 2016
First version publication date	03 April 2016

Trial information

Trial identification

Sponsor protocol code	N01364

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01954121
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma SA
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 1070
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 +49 2173 48 15 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	30 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate the noninferiority of the efficacy of Levetiracetam (LEV 1000 mg/day) versus Carbamazepine immediate-release (CBZ-IR 400 mg/day) used as monotherapy for at least 6 months. Efficacy will be measured as a primary variable by 6-month seizure freedom in adult subjects (≥16 years of age) who are newly or recently diagnosed with epilepsy and are experiencing Partial Onset Seizures (POS) with or without secondarily generalized seizures.

Protection of trial subjects:

None, population from 16 year-old

Background therapy:

Not applicable

Evidence for comparator:

Active Comparator=carbamazepine. Rationale: golden standard in epilepsy.

Actual start date of recruitment	26 September 2013
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	China: 436
Worldwide total number of subjects	436
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)	28
Adults (18-64 years)	387
From 65 to 84 years	21

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in China in September 2013.

Pre-assignment

Screening details:

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

Period 1

Period 1 title	Overall Study (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:

During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Levetiracetam (LEV) 250 mg bid. During Stabilization and Evaluation Period (27 weeks) LEV was taken bid 500 mg.

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

Dosage and administration details:

250 mg and 500 mg levetiracetam tablets

Arm title	Carbamazepine-IR

Arm description:

During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Carbamazepine immediate-release (CBZ-IR) 200 mg qd. During Stabilization and Evaluation (27 weeks) Period CBZ-IR was taken bid 200 mg.

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

Dosage and administration details:

200 mg carbamazepine immediate-release tablets

Number of subjects in period 1	Levetiracetam	Carbamazepine-IR
Started	220	216
Completed	93	125
Not completed	127	91
AE, serious fatal	1	-
Subject did not follow instructions	-	2
Consent withdrawn by subject	18	12
Non-compliant with study procedures	1	-
Pregnancy	1	1
AE, non-serious non-fatal	5	22
Non-compliant patient	1	1
Lost to follow-up	5	6
SAE, non-fatal	1	4
Lack of efficacy	94	41
Protocol deviation	-	2

Baseline characteristics

Subject analysis sets	
Subject analysis set title	Levetiracetam (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Levetiracetam (LEV) 250 mg bid. During Stabilization and Evaluation Period (27 weeks) LEV was taken bid 500 mg.	
Subject analysis set title	Carbamazepine-IR (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Carbamazepine immediate-release (CBZ-IR) 200 mg qd. During Stabilization and Evaluation (27 weeks) Period CBZ-IR was taken bid 200 mg.	
Subject analysis set title	Levetiracetam (Per Protocol Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Levetiracetam (LEV) 250 mg bid. During Stabilization and Evaluation Period (27 weeks) LEV was taken bid 500 mg.	
Subject analysis set title	Carbamazepine-IR (Per Protocol Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Carbamazepine immediate-release (CBZ-IR) 200 mg qd. During Stabilization and Evaluation (27 weeks) Period CBZ-IR was taken bid 200 mg.	

Reporting group values	Levetiracetam (Safety Set)	Carbamazepine-IR (Safety Set)	Levetiracetam (Per Protocol Set)
Number of subjects	218	215	186
Age Categorical			
Units: Subjects			
<=18 years	20	22	
Adults (18-64 years)	184	186	
>=65 years	14	7	
Age Continuous			
Units: years			
arithmetic mean	37.8	33.3	
standard deviation	± 16.2	± 14.3	±
Gender Categorical			
Units: Subjects			
Male	112	121	
Female	106	94	

Reporting group values	Carbamazepine-IR (Per Protocol Set)		
Number of subjects	171		
Age Categorical			
Units: Subjects			
<=18 years			
Adults (18-64 years)			

>=65 years			

Age Continuous Units: years arithmetic mean standard deviation	±		
Gender Categorical Units: Subjects			
Male Female			

End points

End points reporting groups

Reporting group title	Levetiracetam
Reporting group description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Levetiracetam (LEV) 250 mg bid. During Stabilization and Evaluation Period (27 weeks) LEV was taken bid 500 mg.	
Reporting group title	Carbamazepine-IR
Reporting group description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Carbamazepine immediate-release (CBZ-IR) 200 mg qd. During Stabilization and Evaluation (27 weeks) Period CBZ-IR was taken bid 200 mg.	
Subject analysis set title	Levetiracetam (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Levetiracetam (LEV) 250 mg bid. During Stabilization and Evaluation Period (27 weeks) LEV was taken bid 500 mg.	
Subject analysis set title	Carbamazepine-IR (Safety Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Carbamazepine immediate-release (CBZ-IR) 200 mg qd. During Stabilization and Evaluation (27 weeks) Period CBZ-IR was taken bid 200 mg.	
Subject analysis set title	Levetiracetam (Per Protocol Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Levetiracetam (LEV) 250 mg bid. During Stabilization and Evaluation Period (27 weeks) LEV was taken bid 500 mg.	
Subject analysis set title	Carbamazepine-IR (Per Protocol Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Carbamazepine immediate-release (CBZ-IR) 200 mg qd. During Stabilization and Evaluation (27 weeks) Period CBZ-IR was taken bid 200 mg.	

Primary: Proportion of subjects remaining seizure free during the 6-months Evaluation Period

End point title	Proportion of subjects remaining seizure free during the 6-months Evaluation Period
End point description:	
End point type	Primary
End point timeframe:	
6-months Evaluation Period (From Week 4 to Week 30)	

End point values	Levetiracetam (Per Protocol Set)	Carbamazepine -IR (Per Protocol Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	186	171		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	47.3	68.4		

Statistical analyses

Statistical analysis title	Stasticial Analysis 1

Statistical analysis description:

The adjusted absolute difference in treatment group seizure-free proportions (referenced as 'Adjusted difference in proportions' in 'Method of Estimation' below) was derived from the adjusted treatment group proportions of seizure-free subjects. The adjusted proportions were derived from a logistic regression model of seizure freedom using treatment and the categories for the number of seizures in the 3-month period prior to Visit 1 (≤2 seizures and >2 seizures) as covariates.

Comparison groups	Levetiracetam (Per Protocol Set) v Carbamazepine-IR (Per Protocol Set)
Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	adjusted difference in proportions
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.1
upper limit	-12.6

Notes:

[1] - The non-inferiority margin for the adjusted difference in seizure free proportion in the LEV minus the seizure free proportion in the CBZ-IR group was set to absolute -20% points.

Secondary: Proportion of subjects retained in the study for the duration of the period covering the Up Titration Period, Stabilization Period, and Evaluation Period

End point title	Proportion of subjects retained in the study for the duration of the period covering the Up Titration Period, Stabilization Period, and Evaluation Period

End point description:

End point type	Secondary

End point timeframe:

From Week 1 to Week 30

End point values	Levetiracetam (Per Protocol Set)	Carbamazepine -IR (Per Protocol Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	186	171		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	48.4	70.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first seizure or discontinuation due to an Adverse Event (AE) / Lack of Efficacy (LOE) during the Evaluation Period

End point title	Time to first seizure or discontinuation due to an Adverse Event (AE) / Lack of Efficacy (LOE) during the Evaluation Period

End point description:

Number of qualifying events is reported because it is the only descriptive measure available from the proportional hazards model, that was applied.

End point type	Secondary

End point timeframe:

From first day in the Evaluation Period (Week 4) up to end of the Evaluation Period (Week 30)

End point values	Levetiracetam (Per Protocol Set)	Carbamazepine -IR (Per Protocol Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	186	171		
Units: number				
number (not applicable)				
Number of qualifying events	88	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first seizure during the Evaluation Period

End point title	Time to first seizure during the Evaluation Period

End point description:

Number of qualifying events is reported because it is the only descriptive measure available from the proportional hazards model, that was applied.

End point type	Secondary

End point timeframe:

From first day in the Evaluation Period (Week 4) up to end of the Evaluation Period (Week 30)

End point values	Levetiracetam (Per Protocol Set)	Carbamazepine -IR (Per Protocol Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	186	171		
Units: number				
number (not applicable)				
Number of qualifying events	87	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first seizure during the period covering the Up Titration Period, Stabilization Period, and Evaluation Period from the first dose of study drug

End point title	Time to first seizure during the period covering the Up Titration Period, Stabilization Period, and Evaluation Period from the first dose of study drug

End point description:

Number of qualifying events is reported because it is the only descriptive measure available from the proportional hazards model, that was applied.

End point type	Secondary

End point timeframe:

From Randomization (Week 1) up to Evaluation Visit (Week 30)

End point values	Levetiracetam (Per Protocol Set)	Carbamazepine -IR (Per Protocol Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	186	171		
Units: number				
number (not applicable)				
Number of qualifying events	97	57		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from Visit 1 (Week 0) until Safety Follow Up Visit (Week 35).

Adverse event reporting additional description:

Adverse Events refer to the Safety Set (SS), which is a subset of the Randomized Set and consisted of all subjects who received at least 1 dose of study medication after randomization, either Levetiracetam or Carbamezepine immediate-release.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Carbamazepine-IR (Safety Set)

Reporting group description:

During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Carbamazepine immediate-release (CBZ-IR) 200 mg qd. During Stabilization and Evaluation (27 weeks) Period CBZ-IR was taken bid 200 mg.

Reporting group title	Levetiracetam (Safety Set)

Reporting group description:

During the Up-Titration period (2 weeks), subjects initiated treatment at half the randomized target dose with Levetiracetam (LEV) 250 mg bid. During Stabilization and Evaluation Period (27 weeks) LEV was taken bid 500 mg.

Serious adverse events	Carbamazepine-IR (Safety Set)	Levetiracetam (Safety Set)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 215 (5.12%)	9 / 218 (4.13%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	0 / 215 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			

subjects affected / exposed	0 / 215 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epidural haemorrhage			
subjects affected / exposed	0 / 215 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 215 (0.47%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (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 / 215 (0.47%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	2 / 215 (0.93%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	1 / 215 (0.47%)	2 / 218 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 215 (0.47%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	0 / 215 (0.00%)	1 / 218 (0.46%)	
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 / 215 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenic purpura			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (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			
Menopausal symptoms			
subjects affected / exposed	0 / 215 (0.00%)	1 / 218 (0.46%)	
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			
Drug eruption			

subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 218 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 215 (0.47%)	0 / 218 (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-IR (Safety Set)	Levetiracetam (Safety Set)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 215 (43.26%)	92 / 218 (42.20%)	
Investigations			
Blood cholesterol increased			
subjects affected / exposed	11 / 215 (5.12%)	6 / 218 (2.75%)	
occurrences (all)	11	6	
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 215 (5.12%)	2 / 218 (0.92%)	
occurrences (all)	11	2	
White blood cell count decreased			
subjects affected / exposed	11 / 215 (5.12%)	1 / 218 (0.46%)	
occurrences (all)	14	1	
Nervous system disorders			

Dizziness			
subjects affected / exposed	18 / 215 (8.37%)	33 / 218 (15.14%)	
occurrences (all)	29	48	
Somnolence			
subjects affected / exposed	7 / 215 (3.26%)	20 / 218 (9.17%)	
occurrences (all)	8	25	
Headache			
subjects affected / exposed	16 / 215 (7.44%)	19 / 218 (8.72%)	
occurrences (all)	47	33	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	32 / 215 (14.88%)	40 / 218 (18.35%)	
occurrences (all)	42	48	
Upper respiratory tract infection			
subjects affected / exposed	16 / 215 (7.44%)	12 / 218 (5.50%)	
occurrences (all)	18	16	
Urinary tract infection			
subjects affected / exposed	5 / 215 (2.33%)	11 / 218 (5.05%)	
occurrences (all)	5	12	

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