Clinical trial results:
An Open-label, Long Term Follow-up Study With Keppra XR (Levetiracetam XR) for Treatment of Partial-onset Seizures

Summary

EudraCT number	2007-000899-17
Trial protocol	PL
Global end of trial date	31 March 2010

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	24 May 2015

Trial information

Trial identification

Sponsor protocol code	N01281

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00419393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma S.A.
Sponsor organisation address	Chemin du Foriest, Braine-l'Alleud, Belgium, B - 1420
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 June 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide continued treatment of Keppra XR for subjects who participated in the pivotal conversion to monotherapy study (N01280) and to assess the long-term safety of Keppra XR in patients with partial onset seizures.

Protection of trial subjects:

• Dose adjustment due to tolerability
• The ongoing monitoring of safety data was performed to detect as early as possible any safety concern related to the investigational product.

Background therapy:

Not Applicable

Evidence for comparator:

Not Applicable

Actual start date of recruitment	28 February 2008
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	United States: 26
Country: Number of subjects enrolled	Poland: 59
Country: Number of subjects enrolled	Russian Federation: 56
Country: Number of subjects enrolled	Mexico: 49
Worldwide total number of subjects	190
EEA total number of subjects	59

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)	27
Adults (18-64 years)	160
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study recruitment began in February 2008 in the United States, Poland, Mexico, and the Russian Federation. The study completed March 2010.

Pre-assignment

Screening details:

Participant Flow refers to the Intent-to-treat (ITT) Population consisting of all subjects who completed an informed consent.

Period 1

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

Arms

Arm title	Keppra XR (Levetiracetam XR)

Arm description:

1000 – 3000 mg/day Keppra XR (LevetiracetamXR), flexible dosing, throughout the duration of the study (planned: approximately 6 months-3 years)

Arm type	Experimental
Investigational medicinal product name	Keppra XR
Investigational medicinal product code	ucb L059
Other name	Keppra XR
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 - 3000 mg/day Keppra XR (Levetiracetam XR), flexible dosing, throughout the duration of the study.

Number of subjects in period 1	Keppra XR (Levetiracetam XR)
Started	190
Completed	166
Not completed	24
AE, serious fatal	1
Consent withdrawn by subject	7
Other: Sponsor request	3
Other: Site closure	1
AE, non-serious non-fatal	1
Other: Subject had temporal lobectomy	1
Other: Other health problems	1
Other: Investigator decision	1
SAE, non-fatal	3

Protocol deviation	5

Baseline characteristics

Reporting groups	
Reporting group title	Keppra XR (Levetiracetam XR)
Reporting group description:	
1000 – 3000 mg/day Keppra XR (LevetiracetamXR), flexible dosing, throughout the duration of the study (planned: approximately 6 months-3 years)	

Reporting group values	Keppra XR (Levetiracetam XR)	Total	
Number of subjects	190	190	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	27	27	
Adults (18-64 years)	160	160	
From 65-84 years	3	3	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	33.44		
standard deviation	± 14.46	-	
Gender Categorical Units: Subjects			
Female	111	111	
Male	79	79	
Region of Enrollment Units: Subjects			
United States	26	26	
Mexico	49	49	
Poland	59	59	
Russian Federation	56	56	

End points

End points reporting groups

Reporting group title	Keppra XR (Levetiracetam XR)

Reporting group description:

1000 – 3000 mg/day Keppra XR (LevetiracetamXR), flexible dosing, throughout the duration of the study (planned: approximately 6 months-3 years)

Subject analysis set title	Efficacy Population Keppra XR
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Analysis Population (EFF) was defined as all subjects in the Safety Population who have at least one efficacy measurement reported (eg, at least one day of seizure diary data) in the N01281 study. All efficacy analyses were performed using the EFF population.

Subject analysis set title	Safety Set Keppra XR
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who received at least one dose of study medication.

Primary: Number of subjects who experienced at least 1 treatment emergent adverse event during the actual Treatment Period (6 months-2 years)

End point title	Number of subjects who experienced at least 1 treatment emergent adverse event during the actual Treatment Period (6 months-2 years)[1]

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.

End point type	Primary

End point timeframe:

Duration of the Treatment Period (6 months-2 years)

Notes:

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

End point values	Safety Set Keppra XR			
Subject group type	Subject analysis set			
Number of subjects analysed	189			
Units: number of subjects				
Number of subjects	126			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who experienced at least 1 serious treatment emergent adverse event during the actual Treatment Period (6 months-2 years)

End point title	Number of subjects who experienced at least 1 serious treatment emergent adverse event during the actual Treatment Period (6 months-2 years)[2]

End point description:

A serious adverse event is any untoward medical occurrences in a subject administered study treatment, whether or not the event is related to treatment, with at least one of the follow outcomes: death, life-threatening, initial inpatient hospitalization or prolongation of hospitalization, significant or persistent disability/incapacity, congenital anomaly/birth defect, or an important medical event that may jeopardize the subject and require a medical/surgical intervention.

End point type	Primary

End point timeframe:

Duration of the Treatment Period (6 months-2 years)

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 study. Results were summarized in tables as descriptive statistics only.

End point values	Safety Set Keppra XR			
Subject group type	Subject analysis set			
Number of subjects analysed	189			
Units: number of subjects				
Number of subjects	22			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects prematurely discontinuing due to a treatment-emergent adverse event during the actual Treatment Period

End point title	Number of subjects prematurely discontinuing due to a treatment-emergent adverse event during the actual Treatment Period[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.

End point type	Primary

End point timeframe:

Duration of the Treatment Period (6 months-2 years)

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 study. Results were summarized in tables as descriptive statistics only.

End point values	Safety Set Keppra XR			
Subject group type	Subject analysis set			
Number of subjects analysed	189			
Units: number of subjects				
Number of subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects remaining on Keppra XR Monotherapy from study entry through 6 months

End point title	Percentage of subjects remaining on Keppra XR Monotherapy from study entry through 6 months

End point description:

Among subjects in the Efficacy (EFF) population entering the study on Keppra XR monotherapy and exposed for at least 6 months, is the percentage of subjects remaining on monotherapy treatment for at least 6 months.

End point type	Secondary

End point timeframe:

Study entry through 6 months

End point values	Safety Set Keppra XR			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: percentage of subjects				
Percentage of subjects	77			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects remaining on Keppra XR monotherapy from study entry through 12 months

End point title	Percentage of subjects remaining on Keppra XR monotherapy from study entry through 12 months

End point description:

Among subjects in the Efficacy (EFF) population entering the study on Keppra XR monotherapy and exposed for at least 6 months, is the percentage of subjects remaining on monotherapy treatment for at least 12 months.

End point type	Secondary

End point timeframe:

Study entry through 12 months

End point values	Efficacy Population Keppra XR			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: percentage of subjects				
number (not applicable)				
Percentage of subjects	65.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to two years	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Keppra XR (Levetiracetam XR)

Reporting group description:

1000 – 3000 mg/day Keppra XR (Levetiracetam XR), flexible dosing, throughout the duration of the study (planned: approximately 6 months-3 years)

Serious adverse events	Keppra XR (Levetiracetam XR)		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 189 (11.64%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy with contraceptive device			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	2 / 189 (1.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Drowning			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anticonvulsant toxicity			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar puncture headache			

subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	4 / 189 (2.12%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Aphasia			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postictal paralysis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cirrhosis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic fibrosis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Anuria			

subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Periostitis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary tuberculosis			
subjects affected / exposed	1 / 189 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Keppra XR (Levetiracetam XR)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 189 (30.16%)		
Nervous system disorders			
Headache			

subjects affected / exposed	26 / 189 (13.76%)		
occurrences (all)	57		
Somnolence			
subjects affected / exposed	15 / 189 (7.94%)		
occurrences (all)	18		
Dizziness			
subjects affected / exposed	10 / 189 (5.29%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 189 (5.29%)		
occurrences (all)	19		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 189 (7.94%)		
occurrences (all)	19		
Influenza			
subjects affected / exposed	14 / 189 (7.41%)		
occurrences (all)	27		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2007	Protocol Amendment 1 provided for administrative changes and added blood urea nitrogen (BUN) to the clinical chemistry assessments to be performed. This amendment was implemented before any subjects were enrolled in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported