Clinical trial results:
A multi-center, double-blind, historical control, randomized conversion to monotherapy study with Keppra XR for treatment of partial onset seizures

Summary

EudraCT number	2007-000897-21
Trial protocol	PL
Global end of trial date	14 September 2009

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	N01280

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00419094
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma, S.A.
Sponsor organisation address	Chemin du Foriest, Braine-l' Alleud, Belgium, 1420
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +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
Sponsor organisation name	UCB, Inc.
Sponsor organisation address	1950 Lake Park Drive, Smyrna, United States, 30080
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +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	06 November 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of Keppra extended release (XR) compared with a historical control, in the conversion to monotherapy treatment of partial onset seizures.

Protection of trial subjects:

Not applicable

Background therapy:

Standard antiepileptic drug (AED) therapy

Evidence for comparator:

Other AEDs based on historical control

Actual start date of recruitment	06 August 2007
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	Mexico: 60
Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Russian Federation: 64
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	228
EEA total number of subjects	67

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	31
Adults (18-64 years)	194
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Efficacy (EFF) population is defined as all subjects in the Intent-to-Treat (ITT) population who enter into the Previous Antiepileptic (AED) Discontinuation (D/C) Phase. The Per Protocol (PP) population consists of all subjects in the EFF population who have no important protocol deviations related to efficacy.

Pre-assignment

Screening details:

Subjects are to be randomized into treatment with either Keppra XR 2000 mg/day or Keppra XR 1000 mg/day in a 3:1 ratio.
303 subjects were screened/enrolled and 228 randomized.

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	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Keppra XR 1000 mg/day

Arm description:

1000 mg/day once daily for 18 weeks (administered as two Keppra XR tablets and two placebo tablets once daily).

Arm type	Experimental
Investigational medicinal product name	Keppra XR
Investigational medicinal product code	Levetriacetam XR
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Keppra XR 1000 mg/day: administered as two Keppra XR tablets and two Placebo tablets once daily
Keppra XR 2000 mg/day: administered as four Keppra XR tablets once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching Placebo Tablet

Arm title	Keppra XR 2000 mg/day

Arm description:

2000 mg/day once daily for 18 weeks (administered as four Keppra XR tablets once daily).

Arm type	Experimental
Investigational medicinal product name	Keppra XR
Investigational medicinal product code	Levetriacetam XR
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Keppra XR 1000 mg/day: administered as two Keppra XR tablets and two Placebo tablets once daily
Keppra XR 2000 mg/day: administered as four Keppra XR tablets once daily

Number of subjects in period 1	Keppra XR 1000 mg/day	Keppra XR 2000 mg/day
Started	57	171
Completed	50	141
Not completed	7	30
Consent withdrawn by subject	1	5
AE, non-serious non-fatal	2	6
Error determining exit criteria	1	-
Lost to follow-up	-	2
SAE, non-fatal	1	1
Patient non-compliant	-	1
No contact for extended period	-	1
Lack of efficacy	1	-
Protocol deviation	1	14

Baseline characteristics

Reporting groups	
Reporting group title	Keppra XR 1000 mg/day
Reporting group description:	
1000 mg/day once daily for 18 weeks (administered as two Keppra XR tablets and two placebo tablets once daily).	
Reporting group title	Keppra XR 2000 mg/day
Reporting group description:	
2000 mg/day once daily for 18 weeks (administered as four Keppra XR tablets once daily).	

Reporting group values	Keppra XR 1000 mg/day	Keppra XR 2000 mg/day	Total
Number of subjects	57	171	228
Age Categorical Units: Subjects			
<=18 years	11	31	42
Between 18 and 65 years	43	140	183
>=65 years	3	0	3
Age Continuous Units: years			
arithmetic mean	33.48	34.31	
standard deviation	± 16.32	± 13.69	-
Gender Categorical Units: Subjects			
Female	33	99	132
Male	24	72	96
Region of Enrollment Units: Subjects			
United States	8	29	37
Mexico	17	43	60
Poland	16	51	67
Russian Federation	16	48	64

End points

End points reporting groups

Reporting group title	Keppra XR 1000 mg/day
Reporting group description:	
1000 mg/day once daily for 18 weeks (administered as two Keppra XR tablets and two placebo tablets once daily).	
Reporting group title	Keppra XR 2000 mg/day
Reporting group description:	
2000 mg/day once daily for 18 weeks (administered as four Keppra XR tablets once daily).	

Primary: The cumulative exit rate at 112 days after the beginning of the previous antiepileptic drug (AED) tapering phase

End point title	The cumulative exit rate at 112 days after the beginning of the previous antiepileptic drug (AED) tapering phase[1]
End point description:	
Cumulative exit rate at day 112, based on the duration between start date of previous AED tapering to the earliest date exit criterion was met; calculated using Kaplan Meier Methods. Subjects prematurely discontinued for reasons unrelated to exit criteria were censored as of last dose of study drug. Subjects who completed without meeting exit criteria were censored at Day 112. Exit criteria include increase in seizure frequency, severity, duration, status epilepticus, or new generalized seizure. Upper 95% 2-sided confidence limit for exit rate is compared to the historical control rate: 0.678.	
End point type	Primary
End point timeframe:	
112 days	

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: Due to system limitations with studies using an external control, the stat. analysis results could not be entered in this section. The stat. analysis for the prim. and sec. efficacy variable was based on a comparison btw the historical control exit rate (0.678) to the upper limit of the 2-sided 95 % CI for the estimated event rate. If the upper limit of the 95 % CI for the estimate of the event rate for the Keppra arm was less than 0.678, the analysis was positive in favor of the Keppra arm.

End point values	Keppra XR 1000 mg/day	Keppra XR 2000 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	158		
Units: proportion of subjects				
number (confidence interval 95%)				
number (95% confidence interval)	(to)	0.375 (0.297 to 0.453)		

Notes:

[2] - Primary Efficacy analysis was conducted for the Keppra XR 2000 mg/day group only.

Statistical analyses

No statistical analyses for this end point

Secondary: The cumulative rate of exit events, which include discontinuation due to exit criteria, withdrawal due to adverse events (AE) and withdrawal due to lack of efficacy, at 112 days after the beginning of previous antiepileptic drug (AED) tapering phase

End point title	The cumulative rate of exit events, which include discontinuation due to exit criteria, withdrawal due to adverse events (AE) and withdrawal due to lack of efficacy, at 112 days after the beginning of previous antiepileptic drug (AED) tapering phase

End point description:

The cumulative exit event rate at Day 112 was calculated using Kaplan Meier methods. The exit event rate estimate was based on the duration between the start date of previous AED tapering to the earliest date an exit event occured. Subjects who prematurely discontinued for reasons unrelated to exit criteria, adverse event, or lack of efficacy were censored as of the last dose of study medication. Subjects who completed the study without having an exit event were censored as of Day 112.

End point type	Secondary

End point timeframe:

112 days

End point values	Keppra XR 1000 mg/day	Keppra XR 2000 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	158		
Units: proportion of subjects				
number (confidence interval 95%)				
number (95% confidence interval)	(to)	0.385 (0.307 to 0.463)		

Notes:

[3] - Evaluated for Keppra XR 2000 mg/day only.

Statistical analyses

No statistical analyses for this end point

Secondary: The cumulative rate of exit events due to any reasons at 112 days after the beginning of previous antiepileptic drug (AED) tapering phase

End point title	The cumulative rate of exit events due to any reasons at 112 days after the beginning of previous antiepileptic drug (AED) tapering phase

End point description:

The cumulative exit event rate at Day 112 was calculated using Kaplan Meier methods. The exit event rate estimate was based on the duration between the start date of previous AED tapering to the earliest date an exit event occured. Subjects who completed the study without having an exit event were censored as of Day 112.

End point type	Secondary

End point timeframe:

112 days

End point values	Keppra XR 1000 mg/day	Keppra XR 2000 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	158		
Units: proportion of subjects				
number (confidence interval 95%)				
number (95% confidence interval)	(to)	0.475 (0.397 to 0.553)		

Notes:

[4] - Evaluated for Keppra XR 2000 mg/day only.

Statistical analyses

No statistical analyses for this end point

Secondary: The Cumulative Exit Rate at 112 days for the Keppra XR 1000 mg group After the Beginning of the Previous Antiepileptic Drug (AED) Tapering Phase

End point title	The Cumulative Exit Rate at 112 days for the Keppra XR 1000 mg group After the Beginning of the Previous Antiepileptic Drug (AED) Tapering Phase

End point description:

Keppra XR 1000 mg arm was not intended for inferential analysis (planned 3 to 1 randomization, Keppra XR 2000 mg: 1000 mg). The Exit Rate was based on the duration between the start date of previous AED tapering to the earliest date an exit crterion was met. Subjects who prematurely discontinued for reasons unrelated to exit criteria were censored as of the last dose of study medication. Subjects who completed the study without meeting an exit criterion were censored as of Day 112.

End point type	Secondary

End point timeframe:

112 days

End point values	Keppra XR 1000 mg/day	Keppra XR 2000 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	0[5]		
Units: proportion of subjects				
number (confidence interval 95%)				
number (95% confidence interval)	0.334 (0.204 to 0.465)	(to)		

Notes:

[5] - Evaluated for Keppra XR 1000 mg/day only.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 29 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Keppra XR 2000 mg/day
Reporting group description:	
2000 mg/day once daily for 18 weeks (administered as four Keppra XR tablets once daily)	
Reporting group title	Keppra XR 1000 mg/day
Reporting group description:	
1000 mg/day once daily for 18 weeks (administered as two Keppra XR tablets and two placebo tablets once daily)	

Serious adverse events	Keppra XR 2000 mg/day	Keppra XR 1000 mg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 171 (7.02%)	2 / 57 (3.51%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
ankle fracture			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
thrombosis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
convulsion			
subjects affected / exposed	4 / 171 (2.34%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
status epilepticus			

subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatitis acute			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
acute psychosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intervertebral disc protrusion			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar spinal stenosis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
pulmonary tuberculosis			

subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyelonephritis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 57 (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	Keppra XR 2000 mg/day	Keppra XR 1000 mg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 171 (50.88%)	33 / 57 (57.89%)	
Nervous system disorders			
somnolence			
subjects affected / exposed	38 / 171 (22.22%)	12 / 57 (21.05%)	
occurrences (all)	40	13	
headache			
subjects affected / exposed	32 / 171 (18.71%)	13 / 57 (22.81%)	
occurrences (all)	55	34	
convulsion			
subjects affected / exposed	20 / 171 (11.70%)	9 / 57 (15.79%)	
occurrences (all)	20	9	
dizziness			
subjects affected / exposed	15 / 171 (8.77%)	3 / 57 (5.26%)	
occurrences (all)	19	4	
General disorders and administration site conditions			
irritablility			
subjects affected / exposed	12 / 171 (7.02%)	3 / 57 (5.26%)	
occurrences (all)	12	3	
Ear and labyrinth disorders			
vertigo			
subjects affected / exposed	7 / 171 (4.09%)	3 / 57 (5.26%)	
occurrences (all)	7	3	
Gastrointestinal disorders			

abdominal pain subjects affected / exposed occurrences (all)	6 / 171 (3.51%) 6	3 / 57 (5.26%) 3	
Infections and infestations nasopharyngitis subjects affected / exposed occurrences (all)	7 / 171 (4.09%) 7	3 / 57 (5.26%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2007	Protocol Amendment 1 (dated 04 Apr 2007) provided for administrative changes, Content changes, and changes to the study design. This amendment was implemented before any subjects were screened for the study. • The content changes tightened the inclusion/exclusion criteria and were reflective of the criteria indicated in the historical control White Paper or Alternative Monotherapy Design in the Treatment of Epilepsy • The inclusion criterion regarding baseline AED use was modified to 'If taking 2 AEDs, 1 of the baseline AEDs should be taken at less than or equal to 50% of the minimum recommended dose.' • The exclusion criteria were modified as follows: • New criterion added: Seizures that are uncountable due to clustering during the 8-week period prior to Screening (Visit 1) and during the 8-week Baseline Period
04 April 2007	• Benzodiazepine use. (Original text: Regular use of benzodiazepines or intake of benzodiazepines on more than an occasional basis [more than average once per week]) • Use of an investigational drug or device in the 4 months preceding randomization • A sensitivity analysis was added to satisfy anticipated requirements from FDA • Additionally, changes were made to the study design. Rather than utilizing a randomization ratio of 1:1, a ratio of 3:1 was used. This changed the planned sample size to 223 subjects (167 in the 2000 mg/day group and 56 in the 1000 mg/day group). The anticipated number of subjects to be screened was changed to 279. For the statistical analysis, only the 2000 mg/day group was planned to be tested against the historical control. The dose of 2000 mg/day was 90% powered
14 April 2008	Protocol Amendment 2 (dated 14 Apr 2008) provided administrative changes, changes to the Inclusion and Exclusion Criteria section, and changes to the Permitted Concomitant Treatments section due to specific wording inadvertently omitted or documented incorrectly on the previous protocol amendment. This amendment was implemented after 64 subjects had been screened for participation in the study. The change to the inclusion criteria was a modification of the amount of baseline AEDs allowed. Amendment 2 allowed 1 of the baseline AEDs to have been taken at less than or equal to 50% of the minimum recommended dose. The wording for the administration of concomitant antiepileptic medications allowed for tapering off to start at Visit 4 because the visit number was incorrectly documented in original protocol. The CRF page entitled "Subject Eligibility (Inclusion Criteria)" was amended to include additional language noted in this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22516508