Clinical trial results:
A double-blind, placebo-controlled, randomized efficacy and safety study of levetiracetam Extended release formulation (LEV XR), administered as 2 x 500 mg LEV XR tablets once daily as add-on therapy in subjects from 12 to 70 years with refractory epilepsy suffering from partial onset seizures.

Summary

EudraCT number	2006-000987-10
Trial protocol	FI
Global end of trial date	30 May 2007

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	11 July 2015

Trial information

Trial identification

Sponsor protocol code	N01235

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00368069
WHO universal trial number (UTN)	-

Notes:

Sponsors

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, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48, clinicaltrials@ucb.com
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, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48, 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	Yes

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of LEV XR 2 x 500 mg/day once daily, using a placebo as control, as adjunctive therapy in the treatment of refractory epilepsy patients 12 to 70 years of age with partial onset seizures.

Protection of trial subjects:

Not applicable

Background therapy:

Standard anti-epileptic Drug (AED) therapy

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 August 2006
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	Brazil: 1
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	India: 51
Country: Number of subjects enrolled	Mexico: 31
Country: Number of subjects enrolled	Russian Federation: 38
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Ukraine: 25
Worldwide total number of subjects	158
EEA total number of subjects	4

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)	16
Adults (18-64 years)	140
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants flow presents all subjects randomized (Baseline Participants). Safety population does not include 2 patients that never took any study medication.

Pre-assignment

Screening details:

The study was conducted in subjects from 12 to 70 years of age with refractory epilepsy suffering from partial onset seizures; no more than three concomitant anti-epileptic drugs (AEDs) per subject were allowed. It was planned to randomize 130 subjects, 65 per treatment Group.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Keppra®

Arm description:

Keppra® extended release formulation (XR)

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

Dosage and administration details:

LEV XR 2 x 500 mg oral tablet

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
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

Number of subjects in period 1	Keppra®	Placebo
Started	79	79
Completed	71	72
Not completed	8	7
AE, serious fatal	1	-
Consent withdrawn by subject	2	1
AE, non-serious non-fatal	1	1
no blood sampling possible	-	1
Lost to follow-up	1	-
SAE, non-fatal	2	1
SAE, non-fatal + AE, non-serious non-fatal	1	-
Lack of efficacy	-	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Keppra®
Reporting group description:	
Keppra® extended release formulation (XR)	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	Keppra®	Placebo	Total
Number of subjects	79	79	158
Age Categorical Units: Subjects			
Adolescents (12-17 years)	7	9	16
Adults (18-64 years)	71	69	140
From 65-84 years	1	1	2
Age Continuous Units: years			
arithmetic mean	33.97	32.38	
standard deviation	± 13.41	± 12.6	-
Gender Categorical Units: Subjects			
Female	27	32	59
Male	52	47	99
Region of Enrollment Units: Subjects			
Mexico	15	16	31
Finland	2	2	4
Ukraine	13	12	25
South Africa	4	4	8
Russian Federation	19	19	38
India	25	26	51
Brazil	1	0	1

End points

End points reporting groups	
Reporting group title	Keppra®
Reporting group description:	
Keppra® extended release formulation (XR)	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Primary: partial onset seizure (POS) frequency per week - Intention-To-Treat (ITT) Population

End point title	partial onset seizure (POS) frequency per week - Intention-To-Treat (ITT) Population
End point description:	
Number of POS over the treatment period standardized to 1 week period.	
End point type	Primary
End point timeframe:	
Treatment period (12 weeks)	

End point values	Keppra®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: seizures per week (log-transformed data)				
least squares mean (standard error)				
least squares mean (standard error)	0.912 (± 0.053)	1.067 (± 0.052)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Treatment difference was assessed through the percent reduction in POS freq/week of Keppra over Placebo by back transformation of the results of the ANCOVA on log data.	
Comparison groups	Keppra® v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
Method	Transf. of ANCOVA results on log data
Parameter estimate	Percent reduction over Placebo
Point estimate	14.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	26

Statistical analysis title	Statistical Analysis 1
Comparison groups	Keppra® v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.301

Primary: partial onset seizure (POS) frequency per week - Per Protocol (PP) Population

End point title	partial onset seizure (POS) frequency per week - Per Protocol (PP) Population
End point description:	
Number of POS over the treatment period standardized to 1 week period	
End point type	Primary
End point timeframe:	
Treatment Period (12 weeks)	

End point values	Keppra®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	69		
Units: seizures per week (log-transformed data)				
least squares mean (standard error)				
least squares mean (standard error)	0.914 (± 0.049)	1.119 (± 0.048)		

Statistical analyses

Statistical analysis title	Statistical Analyisis 2

Statistical analysis description:

Treatment difference was assessed through the percent reduction in POS frequency per week of Keppra over Placebo by back transformation of the results of the ANCOVA on log data

Comparison groups	Keppra® v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
Method	Transf. of ANCOVA results on log data
Parameter estimate	Percent reduction over Placebo
Point estimate	18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.7
upper limit	28.9

Secondary: POS seizure frequency per Week over Baseline and Treatment Period

End point title	POS seizure frequency per Week over Baseline and Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Baseline Period (8 weeks) - Treatment Period (12 weeks)

End point values	Keppra®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: seizures per week				
median (inter-quartile range (Q1-Q3))				
Baseline POS frequency per week	1.8 (1.13 to 4.13)	2.11 (1.33 to 3.26)		
Treatment POS frequency per week	0.99 (0.33 to 2.7)	1.36 (0.92 to 2.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: All (Type I+II+III) seizures frequency per week

End point title	All (Type I+II+III) seizures frequency per week

End point description:

Number of All type Seizures over the treatment period standardized to 1 week period (Type I -Partial Onset Seizures, Type II - Generalized Seizures, Type III - Unclassified Epileptic Seizures)

End point type	Secondary
End point timeframe:	
Treatment period (12 weeks)	

End point values	Keppra®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: seizures per week (log-transformed data)				
least squares mean (standard error)				
least squares mean (standard error)	0.928 (± 0.053)	1.086 (± 0.052)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Treatment difference was assessed through the percent reduction in POS frequency per week of Keppra over Placebo by back transformation of the results of the ANCOVA on log data	
Comparison groups	Keppra® v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
Method	Transf. of ANCOVA results on log data
Parameter estimate	Percent reduction over Placebo
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	26.3

Statistical analysis title	Statistical Analysis 1
Comparison groups	Keppra® v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.158

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.305

Secondary: 50% response in weekly POS frequency

End point title	50% response in weekly POS frequency

End point description:

A subject is considered as a 50% responder in POS if he/she has a >= 50% decrease from Baseline in the POS frequency/week over Treatment period.

End point type	Secondary

End point timeframe:

Treatment period (12 weeks)

End point values	Keppra®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Participants				
Response	34	23		
Non-Response	45	56		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Keppra® v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	3.55

Secondary: Response in weekly POS frequency (categorized into 6 categories according to reduction) over the treatment period of 12 weeks

End point title	Response in weekly POS frequency (categorized into 6 categories according to reduction) over the treatment period of 12 weeks

End point description:

The response is classified according to the percent reduction from baseline in the POS frequency per week over the Treatment Period of 12 weeks duration.

End point type	Secondary

End point timeframe:

over the treatment period (12 weeks)

End point values	Keppra®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Participants				
< -25%	11	13		
-25% - <25%	14	23		
25% - <75%	35	34		
75% - <100%	11	7		
100%	8	2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Keppra® v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Selection Visit (Week 0) until Final Visit (Week 22).

Adverse event reporting additional description:

The Safety population comprised all subjects who were dispensed study medication. This population was used for the analysis of safety data.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

placebo

Reporting group title	Keppra®

Reporting group description:

Keppra® extended release formulation (XR)

Serious adverse events	Placebo	Keppra®	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 79 (2.53%)	6 / 77 (7.79%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 79 (1.27%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Simple partial seizures			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stupor			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Keppra®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 79 (26.58%)	23 / 77 (29.87%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 79 (2.53%)	4 / 77 (5.19%)	
occurrences (all)	2	4	
Headache			

subjects affected / exposed	11 / 79 (13.92%)	5 / 77 (6.49%)	
occurrences (all)	21	8	
Somnolence			
subjects affected / exposed	2 / 79 (2.53%)	6 / 77 (7.79%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	0 / 79 (0.00%)	5 / 77 (6.49%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 79 (2.53%)	4 / 77 (5.19%)	
occurrences (all)	2	5	
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 79 (3.80%)	6 / 77 (7.79%)	
occurrences (all)	3	7	
Nasopharyngitis			
subjects affected / exposed	4 / 79 (5.06%)	5 / 77 (6.49%)	
occurrences (all)	4	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2006	Amendment 1: Incorporated 10-Aug-2006 The Amendment reflected the decision from FDA to use a two-sided test for the primary and secondary efficacy variables. The sample size was increased accordingly for the same power. Details regarding the population pharmacokinetic and plasma analysis were added as requested by FDA. Additionally, explorative efficacy variables were also added. LEV XR is a new formulation under development in order to provide the subjects the convenience of once daily dosing. This is a Phase III therapeutic confirmatory study to evaluate the efficacy and safety of LEV XR, administered as 2 x 500 mg XR tablets once daily as add-on therapy in refractory epilepsy subjects 12 to 70 years with partial onset seizures.

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/19317886

http://www.ncbi.nlm.nih.gov/pubmed/19699156