Clinical trial results:
An open label, multicenter, parallel-group, two-arm study comparing the pharmacokinetics of Keppra XR in children (aged 12-16 years old) with epilepsy and in adults (aged 18-55 years old) with epilepsy

Summary

EudraCT number	2014-004376-39
Trial protocol	Outside EU/EEA
Global end of trial date	16 March 2010

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	12 July 2015

Trial information

Trial identification

Sponsor protocol code	N01340

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00961441
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES, Inc.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, 27617
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	27 May 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the PK of Keppra XR in children (12 to 16 years old) and adults (18 to 55 years old) with epilepsy.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

Concomitant antiepileptic drugs/ vagus nerve stimulation

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 September 2009
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: 25
Worldwide total number of subjects	25
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)	12
Adults (18-64 years)	13
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Intent-to-treat (ITT) population includes all enrolled patients who received at least one dose of study medication. Pharmacokinetic Per-Protocol (PK-PP) population is a subset of the ITT population, consisting of those patients who had no major protocol deviations affecting the pharmacokinetic parameters.

Pre-assignment

Screening details:

Participant Flow and Baseline characteristics refer to the Intention-to-treat (ITT) population.
Two subjects were excluded from the PK-PP due to study medication noncompliance, one due to wrong dosing regimen.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Keppra XR in Children (12-16 years old)

Arm description:

Drug: Keppra XR Keppra XR 500 mg tablets and Keppra XR 750 mg tablets
Dosage: Keppra XR 1000-3000 mg/day taken once daily
Duration: 4-7 days

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

Dosage and administration details:

Keppra XR 500 mg tablets and Keppra XR 750 mg tablets.
Dosage: Keppra XR 1000-3000 mg/day taken once daily.

Arm title	Keppra XR in Adults (18-55 years old)

Arm description:

Drug: Keppra XR Keppra XR 500 mg tablets and Keppra XR 750 mg tablets
Dosage: Keppra XR 1000-3000 mg/day taken once daily
Duration: 4-7 days

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

Dosage and administration details:

Keppra XR 500 mg tablets and Keppra XR 750 mg tablets.
Dosage: Keppra XR 1000-3000 mg/day taken once daily.

Number of subjects in period 1	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)
Started	12	13
Pharmacokinetic (PK-PP) population	12	10 [1]
Completed	12	13

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Two subjects were excluded due to study medication noncompliance, one due to wrong dosing Regimen.

Baseline characteristics

Reporting groups	
Reporting group title	Keppra XR in Children (12-16 years old)
Reporting group description:	
Drug: Keppra XR Keppra XR 500 mg tablets and Keppra XR 750 mg tablets Dosage: Keppra XR 1000-3000 mg/day taken once daily Duration: 4-7 days	
Reporting group title	Keppra XR in Adults (18-55 years old)
Reporting group description:	
Drug: Keppra XR Keppra XR 500 mg tablets and Keppra XR 750 mg tablets Dosage: Keppra XR 1000-3000 mg/day taken once daily Duration: 4-7 days	

Reporting group values	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)	Total
Number of subjects	12	13	25
Age categorical Units: Subjects			
12-17 years	12	0	12
18-64 years	0	13	13
Age Continuous Units: years			
arithmetic mean	14.88	41.78	
standard deviation	± 1.37	± 9.21	-
Gender Categorical Units: Subjects			
Female	6	8	14
Male	6	5	11
Race Units: Subjects			
Black	4	3	7
Caucasian	8	9	17
Other / mixed	0	1	1
Weight Units: kilogram (kg)			
arithmetic mean	77.2	82.5	
standard deviation	± 24.1	± 23	-
Height Units: centimeter (cm)			
arithmetic mean	165.9	169.3	
standard deviation	± 8.8	± 10.3	-
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	27.62	28.63	
standard deviation	± 7.01	± 7.14	-
Body Surface Area (BSA) Units: m^2			
arithmetic mean	1.87	1.95	
standard deviation	± 0.34	± 0.32	-

End points

End points reporting groups

Reporting group title	Keppra XR in Children (12-16 years old)
Reporting group description:	
Drug: Keppra XR Keppra XR 500 mg tablets and Keppra XR 750 mg tablets Dosage: Keppra XR 1000-3000 mg/day taken once daily Duration: 4-7 days	
Reporting group title	Keppra XR in Adults (18-55 years old)
Reporting group description:	
Drug: Keppra XR Keppra XR 500 mg tablets and Keppra XR 750 mg tablets Dosage: Keppra XR 1000-3000 mg/day taken once daily Duration: 4-7 days	

Primary: Maximum Concentration at Steady State (Cmax) of Keppra XR normalized by dose, and by body weight and dose during up to 7 days of administration

End point title	Maximum Concentration at Steady State (Cmax) of Keppra XR normalized by dose, and by body weight and dose during up to 7 days of administration
End point description:	
The Cmax is the maximum plasma concentration normalized by dose and by body weight and dose. Cmax normalized by 1000 mg dose was calculated as: Cmax/(mg dose taken/ 1000 mg Keppra XR). Cmax normalized by body weight and dose (1 mg Keppra XR/kg) was calculated as: Cmax/(bodyweight (kg)/ mg dose Keppra XR taken). Pharmacokinetic (PK) samples were taken predose and 1h, 2.5h, 4h, 6h and 10h after study medication at day 4, 5, 6 or 7 of Keppra XR administration.	
End point type	Primary
End point timeframe:	
6 pharmacokinetic samples were taken pre-dose, 1, 2.5, 4, 6 and 10 hours after administration, at Day 4, 5, 6, or 7 of Keppra XR administration.	

End point values	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Dose norm. (Keppra XR 1000mg)	17.3 (14.3 to 21)	14.9 (12.1 to 18.5)		
Dose and weight norm. (Keppra XR 1 mg/kg)	1.27 (1.12 to 1.44)	1.24 (1.08 to 1.42)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

An ANOVA for log-transformed values has been used as the basis for calculation of point estimates and Confidence Intervals (CIs). Point estimates for the geometric means ratios children/adults for Cmax normalized by dose and Body weight and 90% CIs have been calculated.

Comparison groups	Keppra XR in Children (12-16 years old) v Keppra XR in Adults (18-55 years old)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Point estimate for ratio
Point estimate	1.0271
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8817
upper limit	1.1964

Primary: Area Under the Plasma Concentration Curve over a dosing interval of 24 hours (AUCtau) of Keppra XR normalized by dose, and by body weight and dose during up to 7 days of administration

End point title	Area Under the Plasma Concentration Curve over a dosing interval of 24 hours (AUCtau) of Keppra XR normalized by dose, and by body weight and dose during up to 7 days of administration

End point description:

AUCtau normalized by 1000 mg dose was calculated as:
AUCtau/(mg dose taken/ 1000 mg Keppra XR).
AUCtau normalized by body weight and dose (1 mg Keppra XR/kg) was calculated as:
AUCtau/(bodyweight (kg)/ mg dose Keppra XR taken).
6 PK samples were taken pre-dose, 1, 2.5, 4, 6 and 10 hours after administration, at Day 4, 5, 6, or 7 of Keppra XR administration. At steady state, reached after 2 days of administration of Keppra XR, the concentrations at 24h postdose is equal to the predose concentration. The predose concentration was used as the 24h concentration to calculate AUCτau.

End point type	Primary

End point timeframe:

6 pharmacokinetic samples were taken pre-dose, 1, 2.5, 4, 6 and 10 hours after administration, at Day 4, 5, 6, or 7 of Keppra XR administration.

End point values	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: µg*h/mL				
geometric mean (confidence interval 95%)				
Dose norm. (Keppra XR 1000mg)	265 (214 to 327)	236 (187 to 298)		
Dose and weight norm. (Keppra XR 1 mg/kg)	19.4 (16.5 to 22.9)	19.6 (16.4 to 23.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

An ANOVA for log-transformed values has been used as the basis for calculation of point estimates and Confidence Intervals (CIs).
Point estimates for the geometric means ratios children/adults for AUCtau normalized by dose and body weight and 90% CIs have been calculated.

Comparison groups	Keppra XR in Children (12-16 years old) v Keppra XR in Adults (18-55 years old)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Point estimate for ratio
Point estimate	0.9914
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.811
upper limit	1.2118

Primary: Time of Maximum Plasma Concentration (Tmax) of Keppra XR during up to 7 days of administration

End point title	Time of Maximum Plasma Concentration (Tmax) of Keppra XR during up to 7 days of administration[1]

End point description:

The Tmax is the time corresponding to the maximum plasma concentration of Keppra XR. It was directly obtained from the observed concentration versus time curve.6 pharmacokinetic samples were taken pre-dose, 1, 2.5, 4, 6 and 10 hours after administration, at Day 4, 5, 6, or 7 of Keppra XR administration.

End point type	Primary

End point timeframe:

6 pharmacokinetic samples were taken pre-dose, 1, 2.5, 4, 6 and 10 hours after administration, at Day 4, 5, 6, or 7 of Keppra XR administration.

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 primary outcome. Results were summarized in tables as descriptive statistics only.

End point values	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: hours (h)				
median (full range (min-max))				
median (full range)	5.9 (2.5 to 6.07)	5.93 (2.45 to 6.05)		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Total Body Clearance (CL/F) of Keppra XR during up to 7 days of administration

End point title	Apparent Total Body Clearance (CL/F) of Keppra XR during up to 7 days of administration[2]

End point description:

The Apparent Total Body Clearance (CL/F) was calculated as Dose/ AUCtau. 6 pharmacokinetic samples were taken pre-dose, 1, 2.5, 4, 6 and 10 hours after administration, at Day 4, 5, 6, or 7 of Keppra XR administration.

End point type	Primary

End point timeframe:

6 pharmacokinetic samples were taken pre-dose, 1, 2.5, 4, 6 and 10 hours after administration, at Day 4, 5, 6, or 7 of Keppra XR administration.

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 primary outcome. Results were summarized in tables as descriptive statistics only.

End point values	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	10		
Units: L/h				
geometric mean (geometric coefficient of variation)				
geometric mean (GeoCV(%))	3.78 (± 31.4)	4.23 (± 41.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Treatment-Emergent Adverse Events from Starting Study Drug Treatment (Day 1) to up to 14 days

End point title	Occurrence of Treatment-Emergent Adverse Events from Starting Study Drug Treatment (Day 1) to up to 14 days

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. Treatment emergent means that an AE has begun or got worse after start of Keppra XR administration.

End point type	Secondary

End point timeframe:

From Starting Study Drug Treatment (Day 1) to up to 14 days

End point values	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: Count				
number (not applicable)				
Total number of AEs	7	11		
Patients with at least 1 AE	3	3		
Patients with severe AEs	0	1		
Patients with serious AEs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Starting Study Drug Treatment (Day 1) to up to 14 days.

Adverse event reporting additional description:

Treatment-Emergent AEs were collected and refer to the Safety Set. Safety Set includes all subjects who took at least one dose of study medication. Treatment emergent means that an Adverse Event has begun or got worse after start of Keppra XR administration.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Keppra XR in Children (12-16 years old)

Reporting group description:

Drug: Keppra XR

Keppra XR 500 mg tablets and Keppra XR 750 mg tablets

Dosage: Keppra XR 1000-3000 mg/day taken once daily

Duration: 4-7 days

Reporting group title	Keppra XR in Adults (18-55 years old)

Reporting group description:

Drug: Keppra XR

Keppra XR 500 mg tablets and Keppra XR 750 mg tablets

Dosage: Keppra XR 1000-3000 mg/day taken once daily

Duration: 4-7 days

Serious adverse events	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Keppra XR in Children (12-16 years old)	Keppra XR in Adults (18-55 years old)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	3 / 13 (23.08%)	

Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Hypoaesthesia facial			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rash			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 13 (7.69%) 1	
Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1	 0 / 13 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0	 1 / 13 (7.69%) 1	
Infections and infestations Pharyngitis streptococcal subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1	 0 / 13 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2009	Protocol Amendment 1 (dated 19 May 2009) was primarily issued to update the Minimum amount of blood to be taken for PK sampling from 1mL to 4mL to ensure that there was enough plasma volume to perform accurate PK analyses. Furthermore, it was clarified that the Final Visit was to take place 7(+3) days after the Evaluation Visit (ie, 7 [+3] days after the final blood sampling) or, if applicable, 7 (+3) days after the Early Discontinuation Visit (EDV) (ie, 7[+3] days after the final administration of Keppra XR). In addition, footnotes in the schedule of study assessments were updated, and clarification was provided regarding the daily record card (DRC), drug accountability, and laboratory measurements. Protocol Amendment 1 was issued prior to any subject being enrolled in N01340 (Listing 13.1).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported