Clinical trial results:
Open-label, Single-arm, Multi-center, Pharmacokinetic, Safety and Tolerability Study of Levetiracetam Intravenous Infusion in Children (1 Month- 4 Years Old) With Epilepsy

Summary

EudraCT number	2007-003517-13
Trial protocol	BE DE FR
Global end of trial date	11 March 2010

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	05 July 2015

Trial information

Trial identification

Sponsor protocol code	N01275

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00505934
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma SA
Sponsor organisation address	Chemin du Foriest, Braine-l'Alleud, Belgium, B-1420
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 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	15 June 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 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 safety and tolerability of the LEV IV 15-minute infusion administered every 12 hours, either as adjunctive treatment or monotherapy in children (1 month to <4 years old) with epilepsy (except status epilepticus), either after switching from the equivalent LEV oral dose administration or as a new antiepileptic treatment.

Protection of trial subjects:

Subjects were hospitalized for the duration of the levetiracetam iv treatment. For the Screening and Final Visit, blood samples were drawn by direct venipuncture using disposable needles. During the treatment period, a catheter may have been used to minimize trauma and speed up sampling. The catheter could have been fitted on the morning of the first day. If not possible, direct venipuncture was performed. EMLA (or other topical anesthetics) could have been used to minimize pain due to puncture or insertion of a catheter. Blood samples must have been taken from another vein than the vein used for the IV infusion.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	16 May 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: 7
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	19
EEA total number of subjects	2

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)	12
Children (2-11 years)	7
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from sites in the United States, Belgium, Germany, France, Mexico, and Turkey. The study began in May 2008 and continued until March 2010, with the last subject's visit occurring in March of 2010.

Pre-assignment

Screening details:

Of the 23 subjects screened, 19 were enrolled into the study and received levetiracetam IV (LEV IV). Participant Flow refers to the Intent-to-treat (ITT) Population, consisting of all subjects who received at least 1 dose of study medication.

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	Levetiracetam

Arm description:

Intravenous 100 mg/mL, twice a day, maximum of 4 days
Subjects on oral levetiracetam at study entry receive the same intravenous (IV) dosage (mg-for-mg) to their oral dose within the following dose range, calculated on the basis of their age and weight:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily) to 42 mg/kg/day (21 mg/kg/day twice daily);
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily) to 60 mg/kg/day (30 mg/kg/day twice daily).
For subjects not taking levetiracetam oral solution prior to entering the study, the intravenous (IV) dosage corresponded to their age and weight as follows:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily).
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily).

Arm type	Experimental
Investigational medicinal product name	Levetiracetam
Investigational medicinal product code	LEV
Other name	Keppra
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous 100 mg/mL, twice a day, maximum of 4 days. Subjects on oral levetiracetam at study entry receive the same intravenous (IV) dosage (mg-for-mg) to their oral dose, calculated on the basis of their age and weight.

Number of subjects in period 1	Levetiracetam
Started	19
Completed	16
Not completed	3
AE, non-serious non-fatal	1
Other: Unable to obtain IV & PK samples	1

Other: IV dose needed to be changed	1

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam

Reporting group description:

Intravenous 100 mg/mL, twice a day, maximum of 4 days
Subjects on oral levetiracetam at study entry receive the same intravenous (IV) dosage (mg-for-mg) to their oral dose within the following dose range, calculated on the basis of their age and weight:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily) to 42 mg/kg/day (21 mg/kg/day twice daily);
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily) to 60 mg/kg/day (30 mg/kg/day twice daily).
For subjects not taking levetiracetam oral solution prior to entering the study, the intravenous (IV) dosage corresponded to their age and weight as follows:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily).
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily).

Reporting group values	Levetiracetam	Total	
Number of subjects	19	19	
Age Categorical Units: Subjects			
<=18 years	19	19	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	1.59		
standard deviation	± 1.24	-	
Gender Categorical Units: Subjects			
Female	7	7	
Male	12	12	
Region of Enrollment Units: Subjects			
United States	7	7	
Mexico	8	8	
Belgium	1	1	
Turkey	2	2	
Germany	1	1	

End points

End points reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Intravenous 100 mg/mL, twice a day, maximum of 4 days
Subjects on oral levetiracetam at study entry receive the same intravenous (IV) dosage (mg-for-mg) to their oral dose within the following dose range, calculated on the basis of their age and weight:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily) to 42 mg/kg/day (21 mg/kg/day twice daily);
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily) to 60 mg/kg/day (30 mg/kg/day twice daily).
For subjects not taking levetiracetam oral solution prior to entering the study, the intravenous (IV) dosage corresponded to their age and weight as follows:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily).
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily).

Primary: Number of subjects reporting at least 1 Treatment-Emergent Adverse Event (TEAE) during the treatment period (up to 4 days)

End point title	Number of subjects reporting at least 1 Treatment-Emergent Adverse Event (TEAE) during the treatment period (up to 4 days)[1]

End point description:

End point type	Primary

End point timeframe:

Treatment period (up to 4 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: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Number of Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who received high-dose levetiracetam intravenous (LEV IV) (more than 28 mg/kg/day for subjects <6 months; >40 mg/kg/day for subjects ≥6 months) during the treatment period (up to 4 days)

End point title	Number of subjects who received high-dose levetiracetam intravenous (LEV IV) (more than 28 mg/kg/day for subjects <6 months; >40 mg/kg/day for subjects ≥6 months) during the treatment period (up to 4 days)

End point description:

End point type	Secondary

End point timeframe:

Treatment period (up to 4 days)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Number of Subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of consecutive levetiracetam intravenous (LEV IV) doses received

End point title	Number of consecutive levetiracetam intravenous (LEV IV) doses received

End point description:

End point type	Secondary

End point timeframe:

Treatment period (up to 4 days)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Consecutive doses				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	2.89 (± 1.41)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4 days

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Intravenous 100 mg/mL, twice a day, maximum of 4 days
Subjects on oral levetiracetam at study entry receive the same intravenous (IV) dosage (mg-for-mg) to their oral dose within the following dose range, calculated on the basis of their age and weight:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily) to 42 mg/kg/day (21 mg/kg/day twice daily);
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily) to 60 mg/kg/day (30 mg/kg/day twice daily).
For subjects not taking levetiracetam oral solution prior to entering the study, the intravenous (IV) dosage corresponded to their age and weight as follows:
• Ages ≥ 1 month to < 6 months: 14 mg/kg/day (7 mg/kg twice daily).
• Ages ≥ 6 months to < 4 years: 20 mg/kg/day (10 mg/kg twice daily).

Serious adverse events	Levetiracetam		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 19 (21.05%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Investigations			
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
CARDIAC ARREST			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
CONVULSION			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
ABDOMINAL SEPSIS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
METABOLIC ACIDOSIS			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		

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

Non-serious adverse events	Levetiracetam		
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 19 (52.63%)		
Investigations ELECTROENCEPHALOGRAM subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Injury, poisoning and procedural complications PROCEDURAL PAIN subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Vascular disorders HYPOTENSION subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Cardiac disorders BRADYCARDIA subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Nervous system disorders SOMNOLENCE subjects affected / exposed occurrences (all) DROOLING subjects affected / exposed occurrences (all) MYOCLONIC EPILEPSY subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 3 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
General disorders and administration site conditions PYREXIA subjects affected / exposed occurrences (all) IRRITABILITY	2 / 19 (10.53%) 2		

subjects affected / exposed occurrences (all) PAIN subjects affected / exposed occurrences (all) PUNCTURE SITE PAIN subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Eye disorders EYE SWELLING subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Gastrointestinal disorders VOMITING subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Respiratory, thoracic and mediastinal disorders RHINORRHOEA subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Skin and subcutaneous tissue disorders PETECHIAE subjects affected / exposed occurrences (all) NEURODERMATITIS subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Psychiatric disorders RESTLESSNESS subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2008	Changes to the protocol included revision of inclusion and exclusion criteria, the schedule of PK assessments as well as some logistical aspects of the study procedures in order to facilitate the recruitment of subjects. The minimum required number of complete sets of PK sampling per maximum 4 days in-patient hospitalization during the Evaluation Period was lowered from 2 sets to 1 set of PK sampling. Also, the sample scheduled to be taken pre-dose was replaced by a sample collected 3-10 minutes after the start of infusion to maximize the number of samples during the Evaluation Period.
18 September 2008	Changes to the protocol included updates to exclusion criteria, administrative changes, clarification of study objectives (main goal of study is safety and tolerability of levetiracetam IV in pediatrics, with a lesser emphasis on PK) and addition of FDA requests that approximately 1/2 of the subjects are exposed to at least 3 consecutive levetiracetam IV doses and at least 1/3 of the subjects should be in the high dose range [i.e. Subjects ≥ 1 month to < 6 months: ≥ 28 mg/kg/day (i.e. 14 mg/kg b.i.d.); subjects ≥ 6 months to < 4 years: ≥ 40 mg/kg/day(i.e. 20 mg/kg b.i.d.)]. Results of simulations of exposure in children from 1 month to 4 years of age performed to evaluate the necessity of a dose adjustment and to establish a nomogram (study N01288) showed that children aged 1 to 6 months would require about 70% of the dose for a 4 year old. Therefore levetiracetam IV dosage was updated.
08 October 2009	Rationale: Changes to the protocol included revision of the inclusion of the age categories to have more balanced age groups (updated categories of 6 subjects ≥1 month to <6months; 6 subjects ≥6 months to <2 years; and 6 subjects ≥2 years to <4 years), clarification of the use of local laboratory and ECG results for the evaluation of subjects' eligibility. Study team members'information was also updated.

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/23533164