

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:

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? Allocation method Blinding used 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).

	31 1 31 31 11
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	1
changed	

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 \geq 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

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: \bullet Ages \geq 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);

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 \geq 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	. 3 70	
	Levelliacetaili		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 19 (52.63%)		
Investigations			
ELECTROENCEPHALOGRAM			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injury, poisoning and procedural			
complications PROCEDURAL PAIN			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
SOMNOLENCE			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
DROOLING			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
MYOCLONIC EPILEPSY			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2 / 19 (10.55 %)		
IRRITABILITY			

	•	
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
PAIN		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
PUNCTURE SITE PAIN		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)		
occurrences (un)	1	
Eye disorders		
EYE SWELLING		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
Gastrointestinal disorders		
VOMITING		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
Respiratory, thoracic and mediastinal disorders		
RHINORRHOEA		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
Skin and subcutaneous tissue disorders PETECHIAE		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
(4.17)	1	
NEURODERMATITIS		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
Psychiatric disorders		
RESTLESSNESS		
subjects affected / exposed	1 / 19 (5.26%)	
occurrences (all)	1	
, ,	<u>.</u>	

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