Clinical trial results:
An Open-label, Single-arm, Multicenter Study to Evaluate the Efficacy and Safety of Adjunctive Treatment With Levetiracetam in Japanese Patients (4 to <16 Years) With Uncontrolled Generalized Tonic-clonic (GTC) Seizures Despite Treatment With 1 or 2 Antiepileptic Drug(s)

Summary

EudraCT number	2014-004382-25
Trial protocol	Outside EU/EEA
Global end of trial date	04 June 2013

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	13 May 2015

Trial information

Trial identification

Sponsor protocol code	N01363

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01292837
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Japan Co. Ltd.
Sponsor organisation address	8-17-1 Nishi-Shinjuku, Tokyo, Japan, 160-0023
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 4815 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 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	09 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of Levetiracetam (LEV) dry syrup at doses up to 60 mg/kg/day or 3000 mg/day used as adjunctive therapy in Japanese pediatric subjects aged ≥ 4 to < 16 years with uncontrolled generalized tonic-clonic (GTC) seizures, despite treatment with 1 or 2 Antiepileptic Drugs (AEDs).

Protection of trial subjects:

Reduced the number of laboratory test to minimise pain and distress.
The pregnancy test performed by urinalysis instead of blood biochemistry, to minimise the blood volume.

Background therapy:

One or two antiepileptic drug(s)

Evidence for comparator:

Not applicable

Actual start date of recruitment	09 February 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 13
Worldwide total number of subjects	13
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)	6

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

Subject disposition

Recruitment

Recruitment details:

This multicenter study started to enroll subjects in Februray 2011 in order to end up with 8 sites in Japan with enrolled subjects.
Participant Flow refers to the Enrolled Set (ES). ES consists of all subjects who signed the consent form and participated in the Prospective Baseline Period.

Pre-assignment

Screening details:

Subjects were screened at 8 sites in Japan. Overall, 13 subjects were screened and enrolled in N01363; there were no screen failures.

Period 1

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

Arms

Arm title	Levetiracetam

Arm description:

Twice daily (morning and evening) orally Levetiracetam: The initial dose is 20 mg/kg/day or 1000 mg/day, divided into two equal dose for the first two weeks, followed by 40 mg/kg/day or 2000 mg/day for two weeks. After reaching 60 mg/kg/day or 3000 mg/day, treatment will continue for 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Levetiracetam
Investigational medicinal product code	ucb L059
Other name	EKeppra
Pharmaceutical forms	Powder for syrup
Routes of administration	Oral use

Dosage and administration details:

The initial dose is 20 mg/kg/day or 1000 mg/day, divided into two equal dose for the first two weeks, followed by 40 mg/kg/day or 2000 mg/day for two weeks. After reaching 60 mg/kg/day or 3000 mg/day, treatment will continue for 20 weeks.

Number of subjects in period 1	Levetiracetam
Started	13
Completed	11
Not completed	2
AE, non-serious non-fatal	1
Further treatment determined	1

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam
Reporting group description:	
Twice daily (morning and evening) orally Levetiracetam: The initial dose is 20 mg/kg/day or 1000 mg/day, divided into two equal dose for the first two weeks, followed by 40 mg/kg/day or 2000 mg/day for two weeks. After reaching 60 mg/kg/day or 3000 mg/day, treatment will continue for 20 weeks.	

Reporting group values	Levetiracetam	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
≥4 to <8 years	4	4	
≥8 to <12 years	2	2	
≥12 to <16 years	7	7	
Age Continuous Units: years			
arithmetic mean	9.7		
standard deviation	± 4.1	-	
Gender Categorical Units: Subjects			
Female	4	4	
Male	9	9	
Region of Enrollment Units: Subjects			
Japan	13	13	
Weight Units: kilogram			
arithmetic mean	32.22		
standard deviation	± 16.56	-	
Body Mass Index Units: kilogram per squaremeter (kg/m^2)			
arithmetic mean	17.89		
standard deviation	± 3.75	-	
Height Units: centimeter			
arithmetic mean	129.36		
standard deviation	± 26.32	-	

End points

End points reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Twice daily (morning and evening) orally Levetiracetam: The initial dose is 20 mg/kg/day or 1000 mg/day, divided into two equal dose for the first two weeks, followed by 40 mg/kg/day or 2000 mg/day for two weeks. After reaching 60 mg/kg/day or 3000 mg/day, treatment will continue for 20 weeks.

Primary: The percent change from the Combined Baseline (4-week Retrospective Baseline and 4-week Prospective Baseline) in the generalized tonic-clonic seizure frequency per week over the 24-week Treatment Period (Up-Titration and Evaluation Periods)

End point title	The percent change from the Combined Baseline (4-week Retrospective Baseline and 4-week Prospective Baseline) in the generalized tonic-clonic seizure frequency per week over the 24-week Treatment Period (Up-Titration and Evaluation Periods)[1]

End point description:

The percent change from Combined Baseline over Treatment Period was calculated from the Generalized Tonic-Clonic (GTC) seizure frequency per week during the Treatment Period (T) and during the Baseline Period (B, Combined Baseline, ie, Retrospective and Prospective Baseline Periods)
using the equation below.

The percent change from Baseline = (B - T)/B x 100

The seizure frequency per week was calculated using the following formula:

Frequency per week of GTC seizures = total number of GTC seizures in the corresponding period / number of days for observation in the corresponding period x 7

End point type	Primary

End point timeframe:

From Baseline (Week -8) to Treatment Period (Week 0 to Week 24)

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: There was no formal statistical hypothesis testing for this endpoint in this open-label, single-arm study. Results were summarized in tables as descriptive statistics only.

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percent change				
arithmetic mean (standard deviation)				
mean (standard deviation)	45.47 (± 50.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: The percent change in generalized tonic-clonic seizure frequency per

week from the Combined Baseline Period over the Evaluation Period	
End point title	The percent change in generalized tonic-clonic seizure frequency per week from the Combined Baseline Period over the Evaluation Period

End point description:

The percent change from Combined Baseline over Evaluation Period was calculated from the Generalized Tonic-Clonic (GTC) seizure frequency per week during the Evaluation Period (E) and during the Baseline Period (B, Combined Baseline, ie, Retrospective and Prospective Baseline Periods) using the equation below.

The percent change from Baseline = (B - E)/B x 100

The seizure frequency per week was calculated using the following formula:

Frequency per week of GTC seizures = total number of GTC seizures in the corresponding period / number of days for observation in the corresponding period x 7

End point type	Secondary

End point timeframe:

From Baseline (Week -8) to Evaluation Period (Week 4 to Week 24)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent change				
arithmetic mean (standard deviation)				
mean (standard deviation)	44.93 (± 51.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Generalized tonic-clonic seizures 50 % responder rate (the proportion of subjects with 50 % or more reduction from the Combined Baseline in the frequency of generalized tonic-clonic seizures) during the Treatment Period	
End point title	Generalized tonic-clonic seizures 50 % responder rate (the proportion of subjects with 50 % or more reduction from the Combined Baseline in the frequency of generalized tonic-clonic seizures) during the Treatment Period

End point description:

The 50 % responder rate during the Treatment Period was the proportion of subjects who reported a ≥ 50 % reduction in seizure frequency per week from Baseline during the Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline (Week -8) to Treatment Period (Week 0 to Week 24)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage of participants				
number (not applicable)				
percentage of participants	53.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Generalized tonic-clonic seizures 50 % responder rate during the Evaluation Period

End point title	Generalized tonic-clonic seizures 50 % responder rate during the Evaluation Period

End point description:

The 50 % responder rate during the Evaluation Period was the proportion of subjects who reported a ≥50 % reduction in seizure frequency per week from Baseline during the Evaluation Period.

End point type	Secondary

End point timeframe:

From Baseline (Week -8) to Evaluation Period (Week 4 to Week 24)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of participants				
number (not applicable)				
percentage of participants	58.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Generalized tonic-clonic seizure freedom over the Treatment Period

End point title	Generalized tonic-clonic seizure freedom over the Treatment Period

End point description:

A subject with a generalized tonic-clonic seizure frequency of 0 per week throughout the Treatment Period was considered a seizure-free subject for that period.

End point type	Secondary

End point timeframe:

Treatment Period (Week 0 to Week 24)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: participants				
participants	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Generalized tonic-clonic seizure freedom over the Evaluation Period

End point title	Generalized tonic-clonic seizure freedom over the Evaluation Period

End point description:

A subject with a generalized tonic-clonic seizure frequency of 0 per week throughout the Evaluation Period was considered a seizure-free subject for that period.

End point type	Secondary

End point timeframe:

Evaluation Period (Week 4 to Week 24)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: participants				
participants	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events were reported from Baseline up to Week 30.

Adverse event reporting additional description:

The Analysis Population refers to the Safety Set. The Safety Set was a subset of the Enrolled Set and consisted of all subjects taking at least 1 dose of the study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Twice daily (morning and evening) orally

Levetiracetam: The initial dose is 20 mg/kg/day or 1000 mg/day, divided into two equal dose for the first two weeks, followed by 40 mg/kg/day or 2000 mg/day for two weeks. After reaching 60 mg/kg/day or 3000 mg/day, treatment will continue for 20 weeks.

Serious adverse events	Levetiracetam		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Levetiracetam		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Arthropod sting			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Subcutaneous haematoma			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Convulsion			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Bradykinesia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	5		
Dental caries			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Respiratory, thoracic and mediastinal disorders			
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Excessive granulation tissue			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Impetigo			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pneumonia mycoplasmal			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2010	• UCB changed the number of the categories for causal relationship of AEs to the study medication to 2 from 4. • UCB changed the standard module of the CRF so that the clinical relevance of the "laboratory abnormalities" was not recorded in the eCRF. • Errors in writing and incorrect information were corrected. • A new Clinical Project Manager was appointed. • There was a need to add some drugs in the list of restricted concomitant drugs and drug brand names were deleted from the lists. • Clarification was provided that the pregnancy test was performed at the investigational site. • The introduction section was updated to reflect that LEV was granted the regulatory approval in Japan after the final protocol was approved.
28 February 2012	The primary purpose of the substantial Protocol Amendment 2 was to extend the study duration and clarify the visit window during the Baseline Period. Changes to the previous edition were required for clarification. The amendment also provided the following changes: • Administrative information was updated. • Two additional prohibited concomitant medications, 1 restricted concomitant medication, and 1 rescue medication, were added. • An additional reference was added.
29 January 2013	The primary purpose of the substantial Protocol Amendment 3 was to extend the study duration and mention the update in approval status by the Food and Drug Administration. The amendment also provided the following changes: • Administrative information was updated. • One additional concomitant antiepileptic medication and 1 restricted concomitant medication were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported