Clinical trial results:
An open-label, multicenter, long-term, follow-up study in Japan to evaluate the safety, tolerability, and efficacy of adjunctive treatment with oral L059 (levetiracetam) in epilepsy subjects with generalized tonic-clonic (GTC) seizures

Summary

EudraCT number	2016-002879-96
Trial protocol	Outside EU/EEA
Global end of trial date	19 April 2016

Results information

Result version number	v1 (current)
This version publication date	15 October 2016
First version publication date	15 October 2016

Trial information

Trial identification

Sponsor protocol code	N01361

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01398956
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Japan Co. Ltd.
Sponsor organisation address	8-17-1 Nishi-shinjuku, Shinjuku-ku, Tokyo, Japan, 160-0023
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, 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 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Provide the Levetiracetam (LEV) treatment to epilepsy subjects in Japan who are judged to benefit from continued treatment with LEV by the investigators and who are willing to continuously receive this drug. Evaluate the safety and tolerability of long-term administration of LEV at doses up to 60 mg/kg/day or 3000 mg/day in epilepsy subjects with generalized tonic-clonic seizures in Japan who have completed the N01159 or N01363 or have discontinued the N01159 due to lack of efficacy.

Protection of trial subjects:

Not applicable

Background therapy:

Antiepileptic drug(s)

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 June 2011
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	Japan: 44
Worldwide total number of subjects	44
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)	8
Adults (18-64 years)	29
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in Japan in June 2011.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set (SS) which consisted of all subjects who took at least one dose of study medication in this study.

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:

Levetiracetam dose will be adjusted at the investigator’s discretion in the range from 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day during this study

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

Dosage and administration details:

Tables in 250 mg and 500 mg concentration

Investigational medicinal product name	E Keppra
Investigational medicinal product code	LEV syrup
Other name	Levetiracetam
Pharmaceutical forms	Granules for syrup
Routes of administration	Oral use

Dosage and administration details:

Dry syrup 50%: 0.5 g Levetiracetam content in 1 g dry syrup

Number of subjects in period 1	Levetiracetam
Started	44
Completed	34
Not completed	10
Consent withdrawn by subject	4
Subject moved a long distance	1
AE, non-serious non-fatal	4
Withdrawal Criteria No.3	1

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam
Reporting group description:	
Levetiracetam dose will be adjusted at the investigator's discretion in the range from 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day during this study	

Reporting group values	Levetiracetam	Total	
Number of subjects	44	44	
Age Categorical Units: Subjects			
>= 24 months - < 12 years	6	6	
>= 12 - < 18 years	8	8	
>=18 - < 65 years	29	29	
>= 65 - < 85 years	1	1	
Age Continuous Units: years			
arithmetic mean	26.1		
standard deviation	± 13.9	-	
Gender Categorical Units: Subjects			
Male	28	28	
Female	16	16	

End points

End points reporting groups

Reporting group title	Levetiracetam
Reporting group description:	
Levetiracetam dose will be adjusted at the investigator's discretion in the range from 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day during this study	
Subject analysis set title	Levetiracetam (SS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Levetiracetam dose will be adjusted at the investigator's discretion in the range from 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day during this study	
Subject analysis set title	Levetiracetam (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Levetiracetam dose will be adjusted at the investigator's discretion in the range from 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day during this study	

Primary: Incidence of treatment emergent adverse events during the entire study period

End point title	Incidence of treatment emergent adverse events during the entire study period[1]
End point description:	
End point type	Primary
End point timeframe:	
Evaluation and Withdrawal Periods	

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 endpoint. Results were summarized in tables as descriptive statistics only.

End point values	Levetiracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: units on a scale				
Number of TEAEs	626			

Statistical analyses

No statistical analyses for this end point

Secondary: The percentage change in Generalized Tonic-Clonic (GTC) seizure frequency per week over the Evaluation Period from either of the Combined Baseline Periods of the previous studies (N01159 or N01363).

End point title	The percentage change in Generalized Tonic-Clonic (GTC) seizure frequency per week over the Evaluation Period from either of the Combined Baseline Periods of the previous studies (N01159 or N01363).

End point description:

End point type	Secondary

End point timeframe:

Baseline of feeder study until end of study

End point values	Levetiracetam (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: units on a scale				
median (confidence interval 95%)				
percent change of combined baseline periods	-92.07 (-97.16 to -64.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: The incidence of adverse drug reactions during the entire study period

End point title	The incidence of adverse drug reactions during the entire study period

End point description:

Adverse drug reactions excludes Adverse Events (AEs) described by the investigators with no relationship to study drug.

End point type	Secondary

End point timeframe:

Evaluation and Withdrawal Periods

End point values	Levetiracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: units on a scale				
Number of ADRs	46			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from Visit 1 (Week 0) until Safety Follow Up Visit.

Adverse event reporting additional description:

Advers events refers to the Safety Set (SS) which consisted of all subjects who took at least one dose of study medication in this study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Levetiracetam (SS)

Reporting group description:

Levetiracetam dose will be adjusted at the investigator's discretion in the range from 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day during this study

Serious adverse events	Levetiracetam (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 44 (29.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Medical observation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast adenoma			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scoliosis surgery			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Monoplegia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status asthmaticus			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fracture malunion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Torticollis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pharyngotonsillitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Levetiracetam (SS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 44 (93.18%)		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Weight increased			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	6		
Protein urine present			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	16		
Excoriation			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	32		

Wound			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Nervous system disorders			
Convulsion			
subjects affected / exposed	16 / 44 (36.36%)		
occurrences (all)	40		
Somnolence			
subjects affected / exposed	10 / 44 (22.73%)		
occurrences (all)	10		
Headache			
subjects affected / exposed	9 / 44 (20.45%)		
occurrences (all)	21		
Dizziness			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	14		
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	5		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Rhinitis allergic			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	6		
Skin erosion			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	6		
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 44 (20.45%)		
occurrences (all)	12		
Nasopharyngitis			
subjects affected / exposed	35 / 44 (79.55%)		
occurrences (all)	138		
Otitis media			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	6		
Bronchitis			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	5		
Gastroenteritis			

subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	11		
Conjunctivitis			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Pulpitis dental			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2012	- Update to the list of restricted concomitant medications; piracetam and pregabalin were added to the list - Update to the section of rescue medication; fosphenytoin sodium hydrate (injection) was added to the section - Administrative changes
29 January 2013	- Update to the section of approval status in Japan and overseas; an approval in Dec 2011 by the Food and Drug Administration (FDA) for LEV as adjunctive treatment in children aged >=1 months was added - Update to the list of concomitant AEDs; stiripentol was added to the list - Update to the list of restricted concomitant medications; paliperidone was added to the list - Administrative changes - Corrections of typographical errors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported