Clinical trial results:
A Double-blind, Multicenter, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Treatment With Oral Levetiracetam, in Epilepsy Patients Aged 16 Years, With Generalized Tonic-clonic (GTC) Seizures

Summary

EudraCT number	2014-004401-32
Trial protocol	Outside EU/EEA
Global end of trial date	27 May 2014

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	N01159

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01228747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Japan Co. Ltd.
Sponsor organisation address	Shinjuku Grand Tower, 8-17-1, Nishi-shinjuku, Shinjuku-ku, Tokyo, Japan, 160-0023
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	30 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Levetiracetam treatment used as adjunctive therapy in Japanese and Chinese epilepsy patients aged ≥ 16 years with uncontrolled generalized tonic-clonic seizures despite treatment with 1 or 2 antiepileptic drug(s).

Protection of trial subjects:

Close monitoring of subjects safety status.

Background therapy:

Anti Epileptic Drugs (AED), as indicated and predefined in the protocol, were allowed as oral administration of 1 or 2 stable concomitant AEDs. For sudden aggravation or cluster seizures and if the subject's condition require rescue medication(s) during minor surgical procedures rescue medication was permitted as specified per protocol.

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 October 2010
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	China: 208
Country: Number of subjects enrolled	Japan: 43
Worldwide total number of subjects	251
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)	15

Adults (18-64 years)	234
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in Japan and China in October 2010.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set consisting of all screened subjects who signed the Informed Consent form, participated in the prospective Baseline Period and were randomized at Visit 2.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	PL1
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo for 28 weeks
Placebo: Matching oral placebo tablets twice daily for 28 weeks

Arm title	Levetiracetam

Arm description:

Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks
Levetiracetam: Oral dose tablets, twice daily

Arm type	Experimental
Investigational medicinal product name	Levetiracetam
Investigational medicinal product code	PR1
Other name	Keppra
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks
Levetiracetam: Oral dose tablets, twice daily

Number of subjects in period 1	Placebo	Levetiracetam
Started	125	126
Completed	60	81
Not completed	65	45
Adverse event, serious fatal	3	-
Consent withdrawn by subject	5	1
Serious adverse event, non-fatal	1	-
Other Reason	2	5
Adverse event, non-serious non-fatal	4	4
Lost to follow-up	4	3
Protocol deviation	6	5
Lack of efficacy	40	27

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks	
Reporting group title	Levetiracetam
Reporting group description:	
Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks Levetiracetam: Oral dose tablets, twice daily	

Reporting group values	Placebo	Levetiracetam	Total
Number of subjects	125	126	251
Age Categorical Units: Subjects			
<=18 years	11	10	21
Between 18 and 65 years	113	115	228
>=65 years	1	1	2
Age Continuous Units: years			
arithmetic mean	32.8	31.5	
standard deviation	± 12.5	± 11.3	-
Gender Categorical Units: Subjects			
Female	49	47	96
Male	76	79	155
Region of Enrollment Units: Subjects			
China	104	104	208
Japan	21	22	43

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks	
Reporting group title	Levetiracetam
Reporting group description:	
Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks Levetiracetam: Oral dose tablets, twice daily	
Subject analysis set title	Levetiracetam Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set consisted of all subjects in the Safety Set who had an evaluable Baseline and at least 1 post-Baseline GTC seizure count data point for the primary efficacy analysis excluding those who had seriously violated GCP. Evaluable Baseline for the primary efficacy analysis: at least 1 GTC seizure was documented for the Combined Baseline.	
Subject analysis set title	Placebo Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set consisted of all subjects in the Safety Set who had an evaluable Baseline and at least 1 post-Baseline GTC seizure count data point for the primary efficacy analysis excluding those who had seriously violated GCP (Good Clinical Practice). Evaluable Baseline for the primary efficacy analysis: at least 1 GTC seizure was documented for the Combined Baseline.	

Primary: Percentage change from the Combined Baseline in the generalized tonic-clonic seizure frequency per week over the 28-week Treatment Period (Dose Adjustment + Evaluation Periods)

End point title	Percentage change from the Combined Baseline in the generalized tonic-clonic seizure frequency per week over the 28-week Treatment Period (Dose Adjustment + Evaluation Periods)
End point description:	
Percentage change in generalized tonic-clonic (GTC) seizure frequency per week from Combined Baseline B over the Treatment Period A is calculated using the equation: Percentage change from Baseline = ((A-B)/B)*100. Percentage change from baseline is not defined for subjects whose baseline information is missing / unknown or equal to zero, or whose seizure frequency per week is missing / unknown. A negative value in change in generalized tonic-clonic (GTC) seizure frequency indicates a reduction of generalized tonic-clonic (GTC) seizure frequency over the 28-week treatment Period. Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline	
End point type	Primary
End point timeframe:	
From Baseline to Week 28	

End point values	Placebo Full Analysis Set	Levetiracetam Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	117		
Units: Percentage Change				
arithmetic mean (standard deviation)				

Overall	-13.19 (± 55.54)	-68.22 (± 34.95)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The statistical hypotheses, null hypothesis (H0) and alternate hypothesis (H1), are stated below:

H0: µLEV = µPBO vs. H1: µLEV ≠ µPBO

ANCOVA on the endpoint "percentage change from Combined Baseline of GTC seizures per week" using "treatment" and "country" as factors (categorical predictors) and "Combined Baseline GTC seizure frequency per week" as a covariate (a continuous predictor) where µLEV and µPBO are adjusted means for LEV and PBO, respectively.

Comparison groups	Placebo Full Analysis Set v Levetiracetam Full Analysis Set
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-56.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.24
upper limit	-44.02
Variability estimate	Standard error of the mean
Dispersion value	6.15

Secondary: The percentage change in generalized tonic-clonic seizure frequency per week from the Combined Baseline over the Evaluation Period

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

End point description:

Percentage change in generalized tonic-clonic (GTC) seizure frequency per week from combined baseline B over the Evaluation Period A is calculated using the equation:
Percentage change from Baseline = ((A-B)/B)*100.
Percentage change from baseline is not defined for subjects whose baseline Information is missing / unknown or equal to zero, or whose seizure frequency per week is missing / unknown. A negative value in change in generalized tonic-clonic (GTC) seizure frequency indicates a reduction of generalized tonic-clonic (GTC) seizure frequency.
Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline.

End point type	Secondary

End point timeframe:

From Baseline to Evaluation Period (Week 12 to Week 28)

End point values	Placebo Full Analysis Set	Levetiracetam Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	108		
Units: Percentage Change				
arithmetic mean (standard deviation)				
Overall	-4.44 (± 153.82)	-68.27 (± 42.63)		

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:

A subject with an at least 50 % reduction in weekly generalized tonic-clonic (GTC) seizure frequency from Combined Baseline Period to the Treatment Period is considered a GTC 50 % responder. Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline

End point type	Secondary

End point timeframe:

From Baseline to Week 28

End point values	Placebo Full Analysis Set	Levetiracetam Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	117		
Units: participants				
Overall	31	91		

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 Evaluation 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 Evaluation Period

End point description:

A subject with an at least 50 % reduction in weekly generalized tonic-clonic (GTC) seizure frequency from Combined Baseline Period to the Evaluation Period is considered a GTC 50 % responder.
Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline

End point type	Secondary

End point timeframe:

From Baseline to Evaluation Period (Week 12 to Week 28)

End point values	Placebo Full Analysis Set	Levetiracetam Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	108		
Units: participants				
Overall	33	82		

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 non-missing weekly generalized tonic-clonic (GTC) baseline seizure frequency and a weekly GTC seizure frequency of zero throughout the Evaluation Period, is considered as a GTC seizure-free subject on the Evaluation Period.

End point type	Secondary

End point timeframe:

Evaluation Period (Week 12 to Week 28)

End point values	Placebo Full Analysis Set	Levetiracetam Full Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	108		
Units: participants				
Overall	3	32		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from the Prospective Baseline Period (Week -8 to Week 0) over Dose Adjustment (12 weeks) and Evaluation Period (16 weeks) until Conversion or Withdrawal Period (4-6 weeks).

Adverse event reporting additional description:

Adverse Events refer to the Safety Set (SS), which is a subset of the Randomized Set and consisted of all subjects who received at least 1 dose of study medication after randomization, either Placebo or Levetiracetam.
Adverse Events were presented for the Dose Adjustment and Evaluation Period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks Levetiracetam: Oral dose tablets, twice daily

Reporting group title	Placebo

Reporting group description:

Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks

Serious adverse events	Levetiracetam	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 126 (0.79%)	4 / 125 (3.20%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	1	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 126 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drowning			
subjects affected / exposed	0 / 126 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sudden unexplained death in epilepsy			

subjects affected / exposed	0 / 126 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Levetiracetam	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 126 (31.75%)	32 / 125 (25.60%)	
Investigations			
Platelet count decreased			
subjects affected / exposed	7 / 126 (5.56%)	4 / 125 (3.20%)	
occurrences (all)	8	4	
Protein urine present			
subjects affected / exposed	10 / 126 (7.94%)	1 / 125 (0.80%)	
occurrences (all)	11	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 126 (3.17%)	9 / 125 (7.20%)	
occurrences (all)	7	14	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 126 (5.56%)	5 / 125 (4.00%)	
occurrences (all)	8	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 126 (19.05%)	20 / 125 (16.00%)	
occurrences (all)	33	36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2010	The substantial Protocol Amendment 1 provided the following major changes: • To detect pregnancy, the sample utilized for the test to detect the level of beta human chorionic gonadotropin (β-hCG) was changed to blood from urine due to issues found in preparation for the central measurements that led to an increase in the volume of the blood sample. • UCB changed the number of the categories for causal relationship of AEs to the study medication from 4 to 2 (“related” or “not related”). • UCB changed the standard module of the eCRF; because of this change, 'laboratory abnormalities that the investigator judges clinically relevant' no longer needed to be recorded in the eCRF. • LEV was granted regulatory approval in Japan after the final protocol was approved.
27 October 2011	The substantial Protocol Amendment 2 provided the following change: the use of commercial Keppra in the Named Patient Program for subjects in China who completed N01159 was clarified. Changes to the previous amendment were required for clarification.
16 February 2012	The substantial Protocol Amendment 3 provided the following changes: the study duration was extended (originally planned from the fourth quarter of 2010 to the first quarter of 2013, extended to the fourth quarter of 2013) and the visit window during the Baseline Period was clarified. Ilepcimide was included in the list of permitted concomitant AEDs.
03 September 2012	The substantial Protocol Amendment 4 provided the following change: the required sample size in Japan was changed based on the progress assessment of the recruitment of the Japanese subjects (originally, 78 subjects were planned for Japan [and 154 subjects in China] and this was changed to 26 subjects in Japan [and 206 subjects in China]). In addition, the study duration was extended to the second quarter of 2014.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported