Clinical trial results:
A randomized, open-label, parallel group, multi-center, comparative, Phase IV trial of Levetiracetam (LEV) versus Topiramate (TPM) as adjunctive therapy to evaluate efficacy and safety in subjects with refractory partial onset seizures

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2014-004402-15
Trial protocol	Outside EU/EEA
Global end of trial date	12 May 2015

Results information

Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	05 February 2016

Trial information

Trial identification

Sponsor protocol code	N01353

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01229735
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Korea Co. Ltd.
Sponsor organisation address	5FL, Grace tower, 127, Teheran-ro, Gangnam-gu, Seoul, Korea, Republic of,
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	10 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term effects of levetiracetam (LEV) on retention rate in subjects with refractory partial onset seizure that are not fully controlled despite optimal treatment with 1 to 3 concomitant antiepileptic drugs (AEDs), compared to topiramate (TPM) as add-on therapy during the 52 week treatment period.

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

In Korea, two of the most commonly prescribed new antiepileptic drugs (AEDs) as add-on therapy for patients with chronic refractory epilepsies are levetiracetam (LEV) and topiramate (TPM) although in a retrospective review, discontinuation of medication due to side effects occurred more often with TPM than LEV. To provide more useful evidence of LEV to clinicians, this study is aiming to compare long term retention rate of levetiracetam (LEV) to topiramate (TPM)

Actual start date of recruitment	17 November 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	Korea, Republic of: 343
Worldwide total number of subjects	343
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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	330
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

447 subjects were screened, 343 subjects were randomized.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set which consists of all subjects who were randomized in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Levetiracetam

Arm description:

250 mg and 500 mg levetiracetam tablet; titration from 1000 mg/day (500 mg bid) to 3000 mg/day (1500 mg bid) levetiracetam with treatment duration up to 52 weeks

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

Dosage and administration details:

250 mg and 500 mg levetiracetam tablets

Arm title	Topiramate

Arm description:

25 mg and 100 mg topiramate tablet; titration from 100 mg/day (50 mg bid) to 400 mg/day (200 mg bid) topiramate with treatment duration up to 52 weeks

Arm type	Active comparator
Investigational medicinal product name	Topiramate
Investigational medicinal product code	TPM
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg and 100 mg topiramate tablets

Number of subjects in period 1	Levetiracetam	Topiramate
Started	177	166
Completed	111	100
Not completed	66	66
Consent withdrawn by subject	18	17
Other Reason	13	10
AE, non-serious non-fatal	13	17
Lost to follow-up	-	2
SAE, non-fatal	-	4
Lack of efficacy	8	8
Protocol deviation	13	8
SAE, non-fatal + AE, non-serious non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam
Reporting group description:	
250 mg and 500 mg levetiracetam tablet; titration from 1000 mg/day (500 mg bid) to 3000 mg/day (1500 mg bid) levetiracetam with treatment duration up to 52 weeks	
Reporting group title	Topiramate
Reporting group description:	
25 mg and 100 mg topiramate tablet; titration from 100 mg/day (50 mg bid) to 400 mg/day (200 mg bid) topiramate with treatment duration up to 52 weeks	

Reporting group values	Levetiracetam	Topiramate	Total
Number of subjects	177	166	343
Age Categorical Units: Subjects			
<=18 years	4	0	4
Adults (18-64 years)	165	162	327
>=65 years	8	4	12
Age Continuous Units: years			
arithmetic mean	40.9	39.7	
standard deviation	± 13.6	± 11.8	-
Gender Categorical Units: Subjects			
Male	106	102	208
Female	71	64	135

End points

End points reporting groups

Reporting group title	Levetiracetam
Reporting group description:	
250 mg and 500 mg levetiracetam tablet; titration from 1000 mg/day (500 mg bid) to 3000 mg/day (1500 mg bid) levetiracetam with treatment duration up to 52 weeks	
Reporting group title	Topiramate
Reporting group description:	
25 mg and 100 mg topiramate tablet; titration from 100 mg/day (50 mg bid) to 400 mg/day (200 mg bid) topiramate with treatment duration up to 52 weeks	
Subject analysis set title	Levetiracetam (Full Analysis Set)
Subject analysis set type	Full analysis
Subject analysis set description:	
250 mg and 500 mg levetiracetam tablet; titration from 1000 mg/day (500 mg bid) to 3000 mg/day (1500 mg bid) levetiracetam with treatment duration up to 52 weeks	
Subject analysis set title	Topiramate (Full Analysis Set)
Subject analysis set type	Full analysis
Subject analysis set description:	
25 mg and 100 mg topiramate tablet; titration from 100 mg/day (50 mg bid) to 400 mg/day (200 mg bid) topiramate with treatment duration up to 52 weeks	
Subject analysis set title	Levetiracetam (Per Protocol Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
250 mg and 500 mg levetiracetam tablet; titration from 1000 mg/day (500 mg bid) to 3000 mg/day (1500 mg bid) levetiracetam with treatment duration up to 52 weeks	
Subject analysis set title	Topiramate (Per Protocol Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
25 mg and 100 mg topiramate tablet; titration from 100 mg/day (50 mg bid) to 400 mg/day (200 mg bid) topiramate with treatment duration up to 52 weeks	

Primary: Percentage of subjects continuing the allocated investigational treatment from the first study treatment intake to Week 52, after the beginning of investigational treatment with levetiracetam compared to topiramate

End point title	Percentage of subjects continuing the allocated investigational treatment from the first study treatment intake to Week 52, after the beginning of investigational treatment with levetiracetam compared to topiramate
End point description:	
End point type	Primary
End point timeframe:	
From Baseline to Week 52	

End point values	Levetiracetam (Full Analysis Set)	Topiramate (Full Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	166		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	59.1	56.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Levetiracetam (Full Analysis Set) v Topiramate (Full Analysis Set)
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.7007 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.7

Notes:

[1] - The Odds Ratio (OR) for LEV vs TPM is based on logistic regression modeling of subject retention by treatment and center pooling category. A profile likelihood confidence interval for the OR is presented.

[2] - P-value is from likelihood ratio test of treatment group regression coefficient against 0.

Secondary: Number of subjects with at least one adverse event reported during the trial period from Baseline to Week 52

End point title	Number of subjects with at least one adverse event reported during the trial period from Baseline to Week 52

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Levetiracetam	Topiramate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	166		
Units: Participants				
Participants	125	128		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from the first study treatment intake to drug discontinuation due to adverse event (AE)

End point title	Time from the first study treatment intake to drug discontinuation due to adverse event (AE)

End point description:

For time to Study Drug Discontinuation due to AE, Kaplan-Meier estimation of event-free subjects does not fall to or below 75%, therefore no first quartile, median or third quartile of the time to event could be estimated in either group.
-99/-999/-9999 = not estimable.

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Levetiracetam	Topiramate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	166		
Units: month				
median (inter-quartile range (Q1-Q3))				
median (inter-quartile range)	-999 (-9999 to -99)	-999 (-9999 to -99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median percent reduction in the weekly partial onset seizure (POS) frequency from Baseline during the total treatment Period from Baseline to Week 52

End point title	Median percent reduction in the weekly partial onset seizure (POS) frequency from Baseline during the total treatment Period from Baseline to Week 52

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Levetiracetam (Full Analysis Set)	Topiramate (Full Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	174	165		
Units: percent reduction				
median (inter-quartile range (Q1-Q3))				
median (inter-quartile range)	74.47 (38 to 96.28)	67.86 (29.21 to 87.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Responders defined as number of subjects with at least 50 % reduction in the weekly POS frequency from baseline during the total treatment period from Baseline to Week 52

End point title	Responders defined as number of subjects with at least 50 % reduction in the weekly POS frequency from baseline during the total treatment period from Baseline to Week 52

End point description:

End point type	Secondary

End point timeframe:

From Baseline to Week 52

End point values	Levetiracetam (Full Analysis Set)	Topiramate (Full Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	174	165		
Units: responders				
participants	120	107		

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 -4) until final Visit 12 (Week 53).	
Adverse event reporting additional description:	
The Safety Set (SS) consisted of all subjects who were randomized and received at least 1 (partial) dose of study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Topiramate
Reporting group description:	
25 mg and 100 mg topiramate tablet; titration from 100 mg/day (50 mg bid) to 400 mg/day (200 mg bid) topiramate with treatment duration up to 52 weeks	
Reporting group title	Levetiracetam
Reporting group description:	
250 mg and 500 mg levetiracetam tablet; titration from 1000 mg/day (500 mg bid) to 3000 mg/day (1500 mg bid) levetiracetam with treatment duration up to 52 weeks	

Serious adverse events	Topiramate	Levetiracetam	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 166 (9.04%)	10 / 177 (5.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Arteriovenous malformation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial septal defect			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 166 (0.00%)	2 / 177 (1.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	5 / 166 (3.01%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stupor			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epilepsy			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Photophobia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Alcoholic pancreatitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			

subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic tonsillitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 177 (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	Topiramate	Levetiracetam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 166 (54.82%)	86 / 177 (48.59%)	
Investigations			

Weight decreased			
subjects affected / exposed	17 / 166 (10.24%)	3 / 177 (1.69%)	
occurrences (all)	19	3	
Nervous system disorders			
Somnolence			
subjects affected / exposed	20 / 166 (12.05%)	36 / 177 (20.34%)	
occurrences (all)	21	40	
Dizziness			
subjects affected / exposed	24 / 166 (14.46%)	30 / 177 (16.95%)	
occurrences (all)	29	47	
Headache			
subjects affected / exposed	24 / 166 (14.46%)	17 / 177 (9.60%)	
occurrences (all)	25	24	
Tremor			
subjects affected / exposed	0 / 166 (0.00%)	9 / 177 (5.08%)	
occurrences (all)	0	9	
Memory impairment			
subjects affected / exposed	9 / 166 (5.42%)	1 / 177 (0.56%)	
occurrences (all)	9	1	
Paraesthesia			
subjects affected / exposed	16 / 166 (9.64%)	2 / 177 (1.13%)	
occurrences (all)	19	2	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	7 / 166 (4.22%)	9 / 177 (5.08%)	
occurrences (all)	8	10	
Nausea			
subjects affected / exposed	10 / 166 (6.02%)	9 / 177 (5.08%)	
occurrences (all)	10	11	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 166 (9.64%)	24 / 177 (13.56%)	
occurrences (all)	22	32	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 166 (15.66%)	3 / 177 (1.69%)	
occurrences (all)	32	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2010	Protocol Amendment 1, dated 02 Sep 2010, created a data safety monitoring plan. The following specific change was provided: The investigator or his/her designee verified the source data after the first case and after every 10 cases to ensure the credibility and quality of the data. No subjects were enrolled prior to the inception of this amendment.
04 November 2010	Protocol Amendment 2, dated 24 Nov 2010, incorporated several suggestions made by the IRB. The following specific changes were provided: - The patient population, inclusion criteria, exclusion criteria, permitted concomitant treatments, and number of participating sites were clarified - The IWRS randomization process was described - The statistical analyses were edited and clarified - Additional information was provided to explain the calculation of sample size Sixteen subjects were enrolled prior to the inception of this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported