



## Clinical trial results:

### **A Double-Blind, Randomized, Multicenter, Placebo-controlled, In-Patient, Maximum 34 Day Study of Levetiracetam Oral Solution (20-50 mg/kg/day) as Adjunctive Treatment of Refractory Partial Onset Seizures in Pediatric Epileptic Subjects Ranging in Age from 1 Month to Less Than 4 Years of Age**

#### **Summary**

EudraCT number	2004-000199-14
Trial protocol	CZ GB BE HU IT
Global end of trial date	26 January 2007

#### **Results information**

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	22 July 2015

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	N01009
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00175890
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	UCB, Inc.
Sponsor organisation address	1950 Lake Park Drive, Smyrna, United States, 30080
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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	22 March 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 January 2007
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the efficacy and safety of levetiracetam (LEV) used as adjunctive treatment in pediatric subjects age 1 month to less than 4 years with refractory partial onset seizures.

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 October 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 7
Worldwide total number of subjects	116
EEA total number of subjects	44

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	61
Children (2-11 years)	55
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:

This double-blind, randomized, multicenter, placebo-controlled, in-Patient study started recruiting in October 2004.

### Pre-assignment

Screening details:

The Intent-to-treat (ITT) Population consisted of all randomized subjects who took at least one dose of study drug.

### 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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Matching oral solution to Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Placebo solution, which is indistinguishable from the Levetiracetam oral solution.

<b>Arm title</b>	Levetiracetam
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Arm description:

10 % oral solution Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.

Arm type	Experimental
Investigational medicinal product name	Levetiracetam (LEV)
Investigational medicinal product code	LEV
Other name	Keppra
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Dosing was stratified by age. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for children one month to less than six months old and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for children 6 month to less than 4 years old, was used in this study. The total daily dose was administered b.i.d.

<b>Number of subjects in period 1</b>	Placebo	Levetiracetam
Started	56	60
Completed	53	58
Not completed	3	2
Protocol deviation	1	-
SAE, non-fatal	1	-
AE, non-serious non-fatal	-	2
Consent withdrawn by subject	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: Matching oral solution to Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.	
Reporting group title	Levetiracetam
Reporting group description: 10 % oral solution Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.	

Reporting group values	Placebo	Levetiracetam	Total
Number of subjects	56	60	116
Age categorical Units: Subjects			
0 - <=27 days	0	0	0
28 days - <24 months	29	32	61
24 months - <12 years	27	28	55
Age Continuous Units: months arithmetic mean standard deviation	23.46 ± 12.06	23.4 ± 13.43	-
Gender Categorical Units: Subjects			
Male	27	30	57
Female	29	30	59
Race/Ethnicity, Customized Units: Subjects			
Caucasian	39	54	93
American Indian or Alaska Native	2	4	6
Other/ mixed race	8	2	10
Black	6	0	6
Asian	1	0	1
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	16	22	38
Not Hispanic or Latino	40	38	78

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Matching oral solution to Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.	
Reporting group title	Levetiracetam
Reporting group description: 10 % oral solution Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.	
Subject analysis set title	Modified Intent-to-Treat (LEV treated Subjects)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable Selection video-EEG time (as determined by a central reader). Furthermore, subjects were included if they met the following criteria: <ul style="list-style-type: none"><li>• At least 24 hours of usable Evaluation video-EEG time, or</li><li>• If &lt; 24 hours of usable Evaluation video-EEG time (including zero time available) and withdrawal from the study with reasons linked to lack or loss of efficacy. These subjects were deemed non-responders (for the primary endpoint).</li></ul>	
Subject analysis set title	Modified Intent-to-Treat (Placebo treated Subjects)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable Selection video-EEG time (as determined by a central reader). Furthermore, subjects were included if they met the following criteria: <ul style="list-style-type: none"><li>• At least 24 hours of usable Evaluation video-EEG time, or</li><li>• If &lt; 24 hours of usable Evaluation video-EEG time (including zero time available) and withdrawal from the study with reasons linked to lack or loss of efficacy. These subjects were deemed non-responders (for the primary endpoint).</li></ul>	
Subject analysis set title	Intent-to-Treat (LEV treated Subjects)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Population consisted of all the randomized subjects who took at least one dose of study drug.	
Subject analysis set title	Subset of mITT (LEV treated Subjects)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects 1 Month to < 6 Months of Age from the mITT. The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable Selection video-EEG time (as determined by a central reader).	
Subject analysis set title	Intent-to-Treat (Placebo treated Subjects)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Population consisted of all the randomized subjects who took at least one dose of study drug.	
Subject analysis set title	Subset of mITT (Placebo treated Subjects)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects 1 Month to < 6 Months of Age from the mITT. The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable Selection video-EEG time (as determined by a central reader).	

**Primary: Responder Rate for total partial onset seizures as computed from the 48-hour Evaluation video-EEG (post-baseline) and the 48-hour Selection video-EEG (baseline)**

End point title	Responder Rate for total partial onset seizures as computed from the 48-hour Evaluation video-EEG (post-baseline) and the 48-hour Selection video-EEG (baseline)
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End point description:

Responder Rate is defined as the number of subjects with a  $\geq 50\%$  reduction from baseline in their Average Daily Frequency (ADF) for partial onset seizures divided by the total number of subjects. If a subject had  $< 24$  hours of usable Evaluation video-EEG time (including zero time available) and withdrawal from the study with reasons linked to lack or loss of efficacy, the subject was counted as a non-responder.

End point type	Primary
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End point timeframe:

48-hours in Evaluation Period and 48-hours in Selection Period

End point values	Modified Intent-to-Treat (Placebo treated Subjects)	Modified Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	58		
Units: percentage of participants				
number (not applicable)				
Responder (percentage)	19.6	43.1		
Non-Responder (percentage)	80.4	56.9		

**Statistical analyses**

Statistical analysis title	Statistical Analysis 1
Comparison groups	Modified Intent-to-Treat (LEV treated Subjects) v Modified Intent-to-Treat (Placebo treated Subjects)
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	8.26

**Secondary: Responder rate for total seizures (all types) as computed from the 48-**



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**hour Evaluation video-EEG (post-baseline) and the 48-hour Selection video-EEG (baseline)**

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End point title	Responder rate for total seizures (all types) as computed from the 48-hour Evaluation video-EEG (post-baseline) and the 48-hour Selection video-EEG (baseline)
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End point description:

Responder Rate is defined as the number of subjects with a  $\geq 50\%$  reduction from baseline in their Average Daily Frequency (ADF) for all seizure types divided by the total number of subjects.

Subjects who withdrew or dropped out before the first 24 hours Evaluation video-EEG with reasons linked to lack of efficacy were considered as non-responders.

All (total) seizures were defined as the total of Type I (partial onset) + Type II (Primary generalized) + Type III (unclassified epileptic).

End point type	Secondary
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End point timeframe:

48-hours in Evaluation Period and 48-hours in Selection Period

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End point values	Modified Intent-to-Treat (Placebo treated Subjects)	Modified Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	58		
Units: percentage of participants				
number (not applicable)				
Responder (percentage)	19.6	43.1		
Non-Responder (percentage)	80.4	56.9		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percent reduction in Average Daily Frequency (ADF) of partial onset seizures recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG**

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End point title	Percent reduction in Average Daily Frequency (ADF) of partial onset seizures recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG
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End point description:

A positive value in Percent reduction from Selection Period to Evaluation Period indicates an improvement.

End point type	Secondary
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End point timeframe:

48-hours in Evaluation Period and 48-hours in Selection Period

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End point values	Modified Intent-to-Treat (Placebo treated Subjects)	Modified Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	55		
Units: Percent reduction				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-20.93 ( $\pm$ 111.47)	24.98 ( $\pm$ 91.49)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent reduction in Average Daily Frequency (ADF) of total seizures (all types) recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG

End point title	Percent reduction in Average Daily Frequency (ADF) of total seizures (all types) recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG
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End point description:

A positive value in Percent reduction from Selection Period to Evaluation Period indicates an improvement.

All (total) seizures were defined as the total of Type I (partial onset) + Type II (Primary generalized) + Type III (unclassified epileptic).

End point type	Secondary
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End point timeframe:

48-hours in Evaluation Period and 48-hours in Selection Period

End point values	Modified Intent-to-Treat (Placebo treated Subjects)	Modified Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	55		
Units: Percent reduction				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-20.93 ( $\pm$ 111.47)	25.08 ( $\pm$ 91.56)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute reduction in Average Daily Frequency (ADF) of partial onset

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**seizures recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG**

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End point title	Absolute reduction in Average Daily Frequency (ADF) of partial onset seizures recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG
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End point description:

A positive value in Absolute reduction from Selection Period to Evaluation Period indicates an improvement.

End point type	Secondary
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End point timeframe:

48-hours in Evaluation Period and 48-hours in Selection Period

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End point values	Modified Intent-to-Treat (Placebo treated Subjects)	Modified Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	58		
Units: Absolute reduction				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-0.86 (± 13.81)	8.54 (± 25.67)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Absolute reduction in Average Daily Frequency (ADF) of total seizures (all types) recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG**

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End point title	Absolute reduction in Average Daily Frequency (ADF) of total seizures (all types) recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG
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End point description:

A positive value in Absolute reduction from Selection Period to Evaluation Period indicates an improvement.

All (total) seizures were defined as the total of Type I (partial onset) + Type II (Primary generalized) + Type III (unclassified epileptic).

End point type	Secondary
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End point timeframe:

48-hours in Evaluation Period and 48-hours in Selection Period

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End point values	Modified Intent-to-Treat (Placebo treated Subjects)	Modified Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	58		
Units: Absolute reduction				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	-0.86 (± 13.81)	9.12 (± 26.35)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent reduction in Average Daily Frequency (ADF) of electro-clinical partial onset seizures recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG for children 1 month to less than 6 months old

End point title	Percent reduction in Average Daily Frequency (ADF) of electro-clinical partial onset seizures recorded on the 48-hour Evaluation video-EEG compared to those recorded on the 48-hour Selection video-EEG for children 1 month to less than 6 months old
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End point description:

A positive value in Percent reduction from Selection Period to Evaluation Period indicates an improvement.

For children 1 month to less than 6 months old, partial onset seizure counts were based on electro-clinical seizures plus electrographic seizures.

End point type	Secondary
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End point timeframe:

48-hours in Evaluation Period and 48-hours in Selection Period

End point values	Subset of mITT (Placebo treated Subjects)	Subset of mITT (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	3		
Units: Percent reduction				
arithmetic mean (standard deviation)				
arithmetic mean (standard deviation)	28.46 (± 44.89)	63.72 (± 28.41)		

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of drop-outs for any reasons during the study**

End point title	Percentage of drop-outs for any reasons during the study
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End point description:

End point type	Secondary
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End point timeframe:

During the study (up to 20 days)

End point values	Intent-to-Treat (Placebo treated Subjects)	Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	60		
Units: percentage of participants				
number (not applicable)				
Drop-outs (percentage)	5.4	3.3		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of drop-outs due to lack of efficacy during the study**

End point title	Percentage of drop-outs due to lack of efficacy during the study
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End point description:

End point type	Secondary
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End point timeframe:

During the study (up to 20 days)

End point values	Intent-to-Treat (Placebo treated Subjects)	Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	60		
Units: percentage of participants				
number (not applicable)				
Drop-outs (percentage)	0	0		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of drop-outs before 24 hours of Evaluation video-EEG for reasons other than lack or loss of efficacy**

End point title	Percentage of drop-outs before 24 hours of Evaluation video-EEG for reasons other than lack or loss of efficacy
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End point description:

End point type	Secondary
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End point timeframe:

During the study (up to 20 days)

End point values	Intent-to-Treat (Placebo treated Subjects)	Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	60		
Units: percentage of participants number (not applicable)				
Drop-outs (percentage)	3.6	1.7		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to Exit (TTE) during the Evaluation Period**

End point title	Time to Exit (TTE) during the Evaluation Period
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End point description:

For early termination subjects in the Evaluation period the TTE is the time to discontinuing the study for any reason. TTE was defined as the day of study discontinuation – the day of randomization + 1. For completed subjects, the TTE was censored on Day 6.

End point type	Secondary
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End point timeframe:

During Evaluation Period (Day 1 to Day 6)

End point values	Intent-to-Treat (Placebo treated Subjects)	Intent-to-Treat (LEV treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56 <sup>[1]</sup>	60 <sup>[2]</sup>		
Units: Days				
median (confidence interval 95%)				
Median (95 % CI)	9999 (999 to 99999)	9999 (999 to 99999)		

Notes:

[1] - 999 / 9999 / 99999 = statistic not estimable

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Selection Period (Day -8 to Day 0) until Post Treatment Follow-up (Day 24  $\pm$  1).

Adverse event reporting additional description:

Adverse Events refer to the Intent-to-treat (ITT) Population, including all randomized subjects who took at least one dose of study drug.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.0
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### Reporting groups

Reporting group title	Levetiracetam
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Reporting group description:

10 % oral solution Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.

Reporting group title	Placebo
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Reporting group description:

Matching oral solution to Levetiracetam b.i.d. (twice a day) for a maximum treatment duration of 20 days.

Serious adverse events	Levetiracetam	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 60 (1.67%)	1 / 56 (1.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 56 (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			
Urinary tract infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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



<b>Non-serious adverse events</b>	Levetiracetam	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 60 (31.67%)	14 / 56 (25.00%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	8 / 60 (13.33%)	1 / 56 (1.79%)	
occurrences (all)	8	1	
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	7 / 60 (11.67%)	0 / 56 (0.00%)	
occurrences (all)	7	0	
Pyrexia			
subjects affected / exposed	2 / 60 (3.33%)	4 / 56 (7.14%)	
occurrences (all)	2	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 60 (1.67%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 60 (3.33%)	3 / 56 (5.36%)	
occurrences (all)	2	4	
Vomiting			
subjects affected / exposed	2 / 60 (3.33%)	3 / 56 (5.36%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 60 (1.67%)	3 / 56 (5.36%)	
occurrences (all)	2	3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2004	Amendment 1 dated 01-Apr-2004 modified the study design to incorporate neuropsychological testing, lengthened the down-titration period to decrease the risk of withdrawal seizures, lengthened the enrollment period and clarified the dosing scheme.
14 February 2005	Amendment 2 dated 14-Feb-2005 defined the policy regarding the enrollment of infants Born pre-term (before 37 weeks gestational age), defined the minimum weight of 4.0 kg and clarified the requirement for pre-screening of subjects by the UCB Clinical Research Physician (CRP).
14 June 2006	Amendment 3 dated 14-Jun-2006 added Argentina, Hungary, Poland, Romania and Russia, updated the background information to reflect FDA and European Commission approval of Keppra® for partial onset seizures in children ages four and above, and studies N159 and N157, defined the distinctive difference between electro-clinical seizure and electrographic seizures, and provided clarity to the description of cluster seizures.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/19243423>