



## 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 |
|-----------------------|--------|

##### **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**

|  |                 |
|--|-----------------|
| 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**

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 | 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 |
| Country: Number of subjects enrolled | United Kingdom: 1     |
| Country: Number of subjects enrolled | United States: 33     |
| 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 |
|------------------|---------------|

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             |
| Consent withdrawn by subject          | 1       | -             |
| AE, non-serious non-fatal             | -       | 2             |
| SAE, non-fatal                        | 1       | -             |
| Protocol deviation                    | 1       | -             |



## Baseline characteristics

### Reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Placebo       |
| Reporting group description:<br>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:<br>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<br>Units: Subjects                                       |                  |                 |       |
| 0 - <=27 days  | 0                | 0               | 0     |
| 28 days - <24 months   | 29               | 32              | 61    |
| 24 months - <12 years  | 27               | 28              | 55    |
| Age Continuous<br>Units: months<br>arithmetic mean<br>standard deviation | 23.46<br>± 12.06 | 23.4<br>± 13.43 | -     |
| Gender Categorical<br>Units: Subjects                                    |                  |                 |       |
| Male   | 27               | 30              | 57    |
| Female   | 29               | 30              | 59    |
| Race/Ethnicity, Customized<br>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<br>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:<br>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:<br>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:<br>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).<br>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:<br>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).<br>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:<br>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:<br>Subjects 1 Month to < 6 Months of Age from the mITT.<br>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:<br>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:<br>Subjects 1 Month to < 6 Months of Age from the mITT.<br>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) |
|-----------------|--|

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 |
|----------------|---------|

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) |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the study (up to 20 days)

| End point values                  | Intent-to-Treat<br>(Placebo<br>treated<br>Subjects) | Intent-to-Treat<br>(LEV treated<br>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 |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the study (up to 20 days)

| End point values                  | Intent-to-Treat<br>(Placebo<br>treated<br>Subjects) | Intent-to-Treat<br>(LEV treated<br>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 |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During the study (up to 20 days)

| End point values                  | Intent-to-Treat<br>(Placebo<br>treated<br>Subjects) | Intent-to-Treat<br>(LEV treated<br>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 |
|-----------------|---|

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 |
|----------------|-----------|

End point timeframe:

During Evaluation Period (Day 1 to Day 6)

| End point values                 | Intent-to-Treat<br>(Placebo<br>treated<br>Subjects) | Intent-to-Treat<br>(LEV treated<br>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)                          |  |  |



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Notes:

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

[2] - 999 / 9999 / 99999 = statistic not estimable

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## Statistical analyses

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 |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |     |
|--------------------|-----|
| Dictionary version | 9.0 |
|--------------------|-----|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| 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 title | Placebo |
|-----------------------|---------|

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                |  |
| 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                |  |
| Psychiatric disorders                                 |                  |                  |  |
| Insomnia  |                  |                  |  |
| subjects affected / exposed                           | 1 / 60 (1.67%)   | 3 / 56 (5.36%)   |  |
| occurrences (all)                                     | 1                | 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>