



Clinical trial results:

An Open-label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of Levetiracetam Used as Monotherapy in Newly or Recently Diagnosed Epilepsy Patients Aged Older Than or Equal to 16 Years With Partial Seizures

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-004377-16 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 14 April 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 July 2016 |
| First version publication date | 30 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | N01375 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01506882 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB Japan Co. Ltd. |
| Sponsor organisation address | 8-17-1 Nishi-Shinjuku, Tokyo, Japan, 160-0023 |
| Public contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 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 | 21 May 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 April 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of LEV used as monotherapy, with efficacy measured as 6-month seizure freedom at the last evaluated dose in the LEV 1000 mg/day to 2000 mg/day group, in newly or recently diagnosed epilepsy subjects.

Protection of trial subjects:

N01375 was continued until the Ministry of Health, Labor and Welfare (Japan) approved the use of Levetiracetam (LEV) monotherapy for Partial Onset Seizures (POS) in adults and until all subjects who were taking LEV as investigational medicinal product (IMP) had a the option to switch to commercial LEV in Japan.

Antidepressant use was allowed if the medication and dose were stable for at least 6 months prior to Visit 1 and the medication and dose were to be kept stable for the entire study duration.

The following medications were used as rescue medications at the investigator's discretion to maintain the subject's safety:

- Diazepam (suppository, injection)
- Phenobarbital sodium (suppository, injection)
- Chloral hydrate (enema preparation, suppository)
- Phenytoin sodium (injection)
- Fosphenytoin sodium hydrate (injection)

Background therapy:

Not applicable

Evidence for comparator:

Based on the controlled studies that evaluated Anti-Epileptic Drugs (AEDs) in the past, the magnitude of the clinical effects of conventional AEDs as the percentage of subjects who achieved 6-month seizure freedom was expected to be approximately 50 % in subjects with newly or recently diagnosed Partial Onset Seizures (POS). The ILAE Treatment Guidelines (Glauser, 2006) stated that non-inferiority outcomes with any relative difference >20 % in the efficacy evaluation had to be regarded as clinically important. According to this, a threshold level of 40 % ($50 \% - 0.2 \times 50 \%$) in efficacy of Levetiracetam (LEV) monotherapy was defined for the percentage of the subjects who would achieve seizure freedom for 6 months by detecting the statistically significant difference between the defined threshold level and the study result to be obtained. The primary efficacy evaluation was to be performed on the LEV 1000 mg/day to 2000 mg/day groups.

| | |
|---|------------------|
| Actual start date of recruitment | 15 December 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 71 |
| Worldwide total number of subjects | 71 |
| 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) | 6 |
| Adults (18-64 years) | 58 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multicenter study started to enroll subjects in December 2011 in order to end up with 27 centers with enrolled subjects in Japan.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set (RS). RS consists of all subjects who were randomized to the study groups.

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 1000 mg/day to 2000 mg/day group |

Arm description:

- Formulation: Tablet- Strength: LEV 250 mg, LEV 500 mg- Dosage: First study dose is 1000 mg/day and if a seizure occurs, the dose will be increased to 2000 mg/day. Max dose in the Follow Up Period is 3000 mg/day.- Frequency: Twice daily

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Levetiracetam |
| Investigational medicinal product code | ucb L059 |
| Other name | Keppra, E Keppra |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

- Active Substance: Levetiracetam
- Pharmaceutical Form: Film-coated tablet
- Concentration: 250 mg and 500 mg
- Route of Administration: Oral use

| | |
|------------------|---------------------------------|
| Arm title | Levetiracetam 3000 mg/day group |
|------------------|---------------------------------|

Arm description:

- Formulation: Tablet- Strength: LEV 250 mg, LEV 500 mg- Dosage: 1000 mg/day for first two weeks, then 2000 mg/day for two weeks then 3000 mg/day by the end of the trial. - Frequency: Twice daily

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Levetiracetam |
| Investigational medicinal product code | ucb L059 |
| Other name | Keppra, E Keppra |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

- Active Substance: Levetiracetam
- Pharmaceutical Form: Film-coated tablet
- Concentration: 250 mg and 500 mg
- Route of Administration: Oral use

| Number of subjects in period 1 | Levetiracetam 1000 mg/day to 2000 mg/day group | Levetiracetam 3000 mg/day group |
|--|--|---------------------------------|
| | | |
| Started | 61 | 10 |
| Completed | 39 | 3 |
| Not completed | 22 | 7 |
| Consent withdrawn by subject | 9 | 3 |
| AE, non-serious non-fatal | 3 | 1 |
| Other Reason | 2 | - |
| Lost to follow-up | 1 | - |
| SAE, non-fatal | 2 | - |
| Lack of efficacy | 4 | 3 |
| SAE, non-fatal + AE, non-serious non-fatal | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Levetiracetam 1000 mg/day to 2000 mg/day group |
|-----------------------|--|

Reporting group description:

- Formulation: Tablet- Strength: LEV 250 mg, LEV 500 mg- Dosage: First study dose is 1000 mg/day and if a seizure occurs, the dose will be increased to 2000 mg/day. Max dose in the Follow Up Period is 3000 mg/day.- Frequency: Twice daily

| | |
|-----------------------|---------------------------------|
| Reporting group title | Levetiracetam 3000 mg/day group |
|-----------------------|---------------------------------|

Reporting group description:

- Formulation: Tablet- Strength: LEV 250 mg, LEV 500 mg- Dosage: 1000 mg/day for first two weeks, then 2000 mg/day for two weeks then 3000 mg/day by the end of the trial. - Frequency: Twice daily

| Reporting group values | Levetiracetam 1000 mg/day to 2000 mg/day group | Levetiracetam 3000 mg/day group | Total |
|---|--|---------------------------------|-------|
| Number of subjects | 61 | 10 | 71 |
| Age Categorical Units: Subjects | | | |
| <=18 years | 10 | 1 | 11 |
| Between 18 and 65 years | 45 | 8 | 53 |
| >=65 years | 6 | 1 | 7 |
| Age Continuous Units: years | | | |
| arithmetic mean | 36.5 | 37 | |
| standard deviation | ± 18 | ± 18.6 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 34 | 4 | 38 |
| Male | 27 | 6 | 33 |
| Region of Enrollment Units: Subjects | | | |
| Japan | 61 | 10 | 71 |
| Weight Units: kilogram (kg) | | | |
| arithmetic mean | 58.98 | 62.58 | |
| standard deviation | ± 12.3 | ± 15.11 | - |
| Height Units: centimeter (cm) | | | |
| arithmetic mean | 161.96 | 166.07 | |
| standard deviation | ± 8.77 | ± 10.21 | - |

End points

End points reporting groups

| | |
|-----------------------|--|
| Reporting group title | Levetiracetam 1000 mg/day to 2000 mg/day group |
|-----------------------|--|

Reporting group description:

- Formulation: Tablet- Strength: LEV 250 mg, LEV 500 mg- Dosage: First study dose is 1000 mg/day and if a seizure occurs, the dose will be increased to 2000 mg/day. Max dose in the Follow Up Period is 3000 mg/day.- Frequency: Twice daily

| | |
|-----------------------|---------------------------------|
| Reporting group title | Levetiracetam 3000 mg/day group |
|-----------------------|---------------------------------|

Reporting group description:

- Formulation: Tablet- Strength: LEV 250 mg, LEV 500 mg- Dosage: 1000 mg/day for first two weeks, then 2000 mg/day for two weeks then 3000 mg/day by the end of the trial. - Frequency: Twice daily

| | |
|----------------------------|--|
| Subject analysis set title | Full Analysis Set (LEV 1000 mg/day to 2000 mg/day group) |
|----------------------------|--|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

FAS includes all subjects in the Safety Set who had at least 1 treatment day in the Evaluation Period. This means that subjects in LEV 1000 to 2000 mg/day group had to have at least 1 treatment day in the Evaluation Period on their final evaluated dose.

- Formulation: Tablet
- Strength: LEV 250 mg, LEV 500 mg
- Dosage: First study dose is 1000 mg/day and if a seizure occurs, the dose will be increased to 2000 mg/day. Max dose in the Follow Up Period is 3000 mg/day.
- Frequency: Twice daily

| | |
|----------------------------|---|
| Subject analysis set title | Full Analysis Set (LEV 3000 mg/day group) |
|----------------------------|---|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

FAS includes all subjects in the Safety Set who had at least 1 treatment day in the Evaluation Period. This means that subjects in LEV 1000 to 2000 mg/day group had to have at least 1 treatment day in the Evaluation Period on their final evaluated dose.

- Formulation: Tablet
- Strength: LEV 250 mg, LEV 500 mg
- Dosage: 1000 mg/day for first two weeks, then 2000 mg/day for two weeks then 3000 mg/day by the end of the trial.
- Frequency: Twice daily

Primary: Percentage of subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group who are seizure free for 26 consecutive weeks of treatment during the Evaluation Period

| | |
|-----------------|---|
| End point title | Percentage of subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group who are seizure free for 26 consecutive weeks of treatment during the Evaluation Period ^[1] |
|-----------------|---|

End point description:

A subject was considered seizure free, if no seizure occurred during the 6 consecutive months (26 weeks) in the Evaluation Period. If one of the following occurred, the subject was not considered seizure free:

- A documented seizure during 6 consecutive months of the Evaluation Analysis Period
- Subject discontinued the study prematurely during the Evaluation Analysis Period
- Missing Seizure Count Case Report Forms (CRFs) prior to completing the Evaluation Analysis Period.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the end of the 1-week Stabilization Period over the 26-weeks Evaluation Period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Values presented below are from the statistical analysis of this Primary Endpoint. The lower limit of the two-sided 95% CI for the estimate of Percentage of subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group who are seizure free for 26 consecutive weeks of treatment during

the Evaluation Period, 60.9%, was greater than the reference value 40%.

| End point values | Levetiracetam 1000 mg/day to 2000 mg/day group | Levetiracetam 3000 mg/day group | | |
|-----------------------------------|---|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 0 ^[2] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| percentage of participants | 73.8 (60.9 to 84.2) | (to) | | |

Notes:

[2] - Primary Efficacy analysis was conducted for the 1000 mg/day - 2000 mg/day group only

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group who are seizure free for 52 consecutive weeks of treatment during the Evaluation Period and the Maintenance Period

| | |
|-----------------|---|
| End point title | Percentage of subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group who are seizure free for 52 consecutive weeks of treatment during the Evaluation Period and the Maintenance Period |
|-----------------|---|

End point description:

Subjects who complete the 26-weeks Evaluation Period without having a seizure will continue receiving the same dose of LEV as in the Evaluation Period during the 26-weeks Maintenance Period unless a seizure occurs.

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

End point timeframe:

From entry in the 26-weeks Evaluation Period to the end of the 26-weeks Maintenance Period

| End point values | Full Analysis Set (LEV 1000 mg/day to 2000 mg/day group) | | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 61 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| percentage of participants | 59 (45.7 to 71.4) | | | |

Statistical analyses

Secondary: Percentage of subjects in the Levetiracetam (LEV) 3000 mg/day group who are seizure free for 26 consecutive weeks of treatment during the Evaluation Period

| | |
|-----------------|--|
| End point title | Percentage of subjects in the Levetiracetam (LEV) 3000 mg/day group who are seizure free for 26 consecutive weeks of treatment during the Evaluation Period ^[3] |
|-----------------|--|

End point description:

A subject was considered seizure free, if no seizure occurred during the 6 consecutive months (26 weeks) in the Evaluation Period. If one of the following occurred, the subject was not considered seizure free:

- A documented seizure during 6 consecutive months of the Evaluation Analysis Period
- Subject discontinued the study prematurely during the Evaluation Analysis Period
- Missing Seizure Count Case Report Forms (CRFs) prior to completing the Evaluation Analysis Period.

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

End point timeframe:

From the end of the 1-week Stabilization Period over the 26-weeks Evaluation Period

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Statistics for the 1000 mg/day to 2000 mg/day group are not reported here as this group was not part of this secondary Endpoint.

| End point values | Levetiracetam 3000 mg/day group | | | |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| percentage of participants | 22.2 (2.8 to 60) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects in the Levetiracetam (LEV) 3000 mg/day group who are seizure free for 52 consecutive weeks of treatment during the Evaluation Period and the Maintenance Period

| | |
|-----------------|--|
| End point title | Percentage of subjects in the Levetiracetam (LEV) 3000 mg/day group who are seizure free for 52 consecutive weeks of treatment during the Evaluation Period and the Maintenance Period |
|-----------------|--|

End point description:

Subjects who complete the 26-weeks Evaluation Period without having a seizure will continue receiving LEV 3000 mg/day during the 26-weeks Maintenance Period unless a seizure occurs.

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

End point timeframe:

From entry in the 26-weeks Evaluation Period to the end of the 26-weeks Maintenance Period

| | | | | |
|-----------------------------------|---|--|--|--|
| End point values | Full Analysis Set (LEV 3000 mg/day group) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 9 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| percentage of participants | 11.1 (0.3 to 48.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first seizure at the last evaluated dose in subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group

| | |
|---|--|
| End point title | Time to first seizure at the last evaluated dose in subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group |
| End point description: | |
| Time was measured from first day of last evaluated dose. Seizures during Stabilization were not considered. | |
| The Median time to first seizure will be estimated from the Kaplan-Meier curve. | |
| End point type | Secondary |
| End point timeframe: | |
| During Evaluation, Maintenance and Safety Follow Up Period after 1-week Stabilization Period, assessed up to 1 year | |

| | | | | |
|--|--|--|--|--|
| End point values | Full Analysis Set (LEV 1000 mg/day to 2000 mg/day group) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 61 ^[4] | | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Median Time to First Seizure (95 % CI) | 999 (359 to 9999) | | | |

Notes:

[4] - 999/9999= Median Time and upper limit of the 95 % CI were not estimable.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to withdrawal at the last evaluated dose in subjects in the

Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group

| | |
|-----------------|---|
| End point title | Time to withdrawal at the last evaluated dose in subjects in the Levetiracetam (LEV) 1000 mg/day to 2000 mg/day group |
|-----------------|---|

End point description:

Median time to withdrawal will be estimated from the Kaplan-Meier curve.

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

End point timeframe:

During 1-week Stabilization Period, Evaluation, Maintenance and Safety Follow Up Period, assessed up to 1 year

| | | | | |
|-------------------------------------|--|--|--|--|
| End point values | Full Analysis Set (LEV 1000 mg/day to 2000 mg/day group) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 61 ^[5] | | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Median Time to Withdrawal (95 % CI) | 999 (99 to 9999) | | | |

Notes:

[5] - 99/999/9999= Median Time and upper and lower limit of the 95 % CI were not estimable.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first seizure in subjects in the Levetiracetam (LEV) 3000 mg/day group

| | |
|-----------------|--|
| End point title | Time to first seizure in subjects in the Levetiracetam (LEV) 3000 mg/day group |
|-----------------|--|

End point description:

Time was measured from first day of last evaluated dose. Seizures during Stabilization were not considered.

The Median time to first seizure will be estimated from the Kaplan-Meier curve.

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

End point timeframe:

During Evaluation, Maintenance and Safety Follow Up Period after 1-week Stabilization Period, assessed up to 1 year

| | | | | |
|--|---|--|--|--|
| End point values | Full Analysis Set (LEV 3000 mg/day group) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 9 ^[6] | | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Median Time to First Seizure (95 % CI) | 106 (9 to 999) | | | |

Notes:

[6] - 999= Upper limit of the 95 % CI was not estimable.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to withdrawal in subjects in the Levetiracetam (LEV) 3000 mg/day group

| | |
|-----------------|--|
| End point title | Time to withdrawal in subjects in the Levetiracetam (LEV) 3000 mg/day group ^[7] |
|-----------------|--|

End point description:

Median time to withdrawal will be estimated from the Kaplan-Meier curve.

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

End point timeframe:

During 1-week Stabilization Period, Evaluation, Maintenance and Safety Follow Up Period, assessed up to 1 year

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics for the 1000 mg/day to 2000 mg/day group are not reported here as this group was not part of this secondary Endpoint.

| | | | | |
|-------------------------------------|---------------------------------|--|--|--|
| End point values | Levetiracetam 3000 mg/day group | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 9 | | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Median Time to Withdrawal (95 % CI) | 91 (21 to 197) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent Adverse Events were collected from Screening (Week 0) over the Evaluation and Maintenance Period (Week 4 to Week 53) until the last Follow-up Visit or Withdrawal Visit.

Adverse event reporting additional description:

Adverse Events refer to the Safety Set including all subjects in the Enrolled Set who received at least 1 dose of the Investigational Medicinal Product.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Levetiracetam 1000 mg/day to 2000 mg/day group |
|-----------------------|--|

Reporting group description:

- Formulation: Tablet
- Strength: LEV 250 mg, LEV 500 mg
- Dosage: First study dose is 1000 mg/day and if a seizure occurs, the dose will be increased to 2000 mg/day. Max dose in the Follow Up Period is 3000 mg/day.
- Frequency: Twice daily

| | |
|-----------------------|---------------------------------|
| Reporting group title | Levetiracetam 3000 mg/day group |
|-----------------------|---------------------------------|

Reporting group description:

- Formulation: Tablet
- Strength: LEV 250 mg, LEV 500 mg
- Dosage: 1000 mg/day for first two weeks, then 2000 mg/day for two weeks then 3000 mg/day by the end of the trial.
- Frequency: Twice daily

| Serious adverse events | Levetiracetam 1000 mg/day to 2000 mg/day group | Levetiracetam 3000 mg/day group | |
|---|--|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 61 (13.11%) | 2 / 10 (20.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Surgical and medical procedures | | | |
| Meniscus removal | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Status epilepticus | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|-----------------|--|
| Postictal state | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 10 (10.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (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 | | | |
| Irritability | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol withdrawal syndrome | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postictal psychosis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kaposi's varicelliform eruption | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 10 (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 1000 mg/day to 2000 mg/day group | Levetiracetam 3000 mg/day group | |
|---|--|---------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 58 / 61 (95.08%) | 10 / 10 (100.00%) | |
| General disorders and administration site conditions | | | |
| Malaise | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>12 / 61 (19.67%)</p> <p>13</p> <p>5 / 61 (8.20%)</p> <p>6</p> | <p>0 / 10 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>2</p> | |
| <p>Reproductive system and breast disorders</p> <p>Dysmenorrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Acquired phimosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 61 (8.20%)</p> <p>8</p> <p>0 / 61 (0.00%)</p> <p>0</p> | <p>0 / 10 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>1</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rhinitis allergic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper respiratory tract inflammation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 61 (8.20%)</p> <p>6</p> <p>1 / 61 (1.64%)</p> <p>1</p> <p>1 / 61 (1.64%)</p> <p>1</p> | <p>0 / 10 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>3</p> <p>1 / 10 (10.00%)</p> <p>1</p> | |
| <p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Attention deficit/hyperactivity disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 61 (1.64%)</p> <p>1</p> <p>0 / 61 (0.00%)</p> <p>0</p> | <p>1 / 10 (10.00%)</p> <p>1</p> <p>1 / 10 (10.00%)</p> <p>1</p> | |
| <p>Investigations</p> <p>Gamma-glutamyltransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight increased</p> | <p>2 / 61 (3.28%)</p> <p>2</p> | <p>1 / 10 (10.00%)</p> <p>1</p> | |

| | | | |
|--|------------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 2 / 10 (20.00%) 2 | |
| Urine ketone body present subjects affected / exposed occurrences (all) | 2 / 61 (3.28%) 2 | 1 / 10 (10.00%) 1 | |
| Blood urine present subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 10 (10.00%) 1 | |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 5 / 61 (8.20%) 6 | 0 / 10 (0.00%) 0 | |
| Head injury subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 2 / 10 (20.00%) 2 | |
| Ligament sprain subjects affected / exposed occurrences (all) | 1 / 61 (1.64%) 1 | 1 / 10 (10.00%) 1 | |
| Arthropod sting subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Mouth injury subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Procedural pain subjects affected / exposed occurrences (all) | 0 / 61 (0.00%) 0 | 1 / 10 (10.00%) 1 | |
| Nervous system disorders | | | |
| Somnolence subjects affected / exposed occurrences (all) | 25 / 61 (40.98%) 32 | 2 / 10 (20.00%) 2 | |
| Dizziness | | | |

| | | | |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 8 / 61 (13.11%) | 1 / 10 (10.00%) | |
| occurrences (all) | 9 | 1 | |
| Headache | | | |
| subjects affected / exposed | 10 / 61 (16.39%) | 1 / 10 (10.00%) | |
| occurrences (all) | 14 | 1 | |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 10 (10.00%) | |
| occurrences (all) | 1 | 1 | |
| Amnestic disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 61 (13.11%) | 2 / 10 (20.00%) | |
| occurrences (all) | 18 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 1 / 10 (10.00%) | |
| occurrences (all) | 14 | 1 | |
| Dental caries | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 0 / 10 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 1 / 10 (10.00%) | |
| occurrences (all) | 4 | 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 10 (0.00%) | |
| occurrences (all) | 17 | 0 | |
| Gastritis | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 10 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Vomiting | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastrooesophageal reflux disease</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lip ulceration</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 61 (6.56%)</p> <p>5</p> <p>1 / 61 (1.64%)</p> <p>1</p> <p>0 / 61 (0.00%)</p> <p>0</p> <p>0 / 61 (0.00%)</p> <p>0</p> | <p>0 / 10 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>1</p> <p>1 / 10 (10.00%)</p> <p>1</p> <p>1 / 10 (10.00%)</p> <p>1</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Eczema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry skin</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 61 (1.64%)</p> <p>1</p> <p>0 / 61 (0.00%)</p> <p>0</p> | <p>1 / 10 (10.00%)</p> <p>2</p> <p>1 / 10 (10.00%)</p> <p>1</p> | |
| <p>Renal and urinary disorders</p> <p>Ketonuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 61 (0.00%)</p> <p>0</p> | <p>1 / 10 (10.00%)</p> <p>1</p> | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Musculoskeletal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 61 (9.84%)</p> <p>7</p> <p>1 / 61 (1.64%)</p> <p>1</p> | <p>0 / 10 (0.00%)</p> <p>0</p> <p>1 / 10 (10.00%)</p> <p>1</p> | |
| <p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>47 / 61 (77.05%)</p> <p>155</p> <p>7 / 61 (11.48%)</p> <p>8</p> | <p>4 / 10 (40.00%)</p> <p>7</p> <p>0 / 10 (0.00%)</p> <p>0</p> | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 10 (10.00%) | |
| occurrences (all) | 3 | 1 | |
| Cystitis | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 10 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 10 (10.00%) | |
| occurrences (all) | 1 | 1 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 10 (10.00%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported