



Clinical trial results:

An Open Label, Single-Arm, Multi-Center Study on the Efficacy, Safety and Pharmacokinetics of Levetiracetam in Pediatric Patients (4 to 16 Years) With Partial Seizures Despite Treatment With 1 or 2 Anti-Epileptic Drugs

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-004335-39 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 24 October 2013 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 30 June 2016 |
| First version publication date | 25 April 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | N01223 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01063764 |
| 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, 0049 2173 4815 15, clinicaltrials@ucb.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 January 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

First Period:

The primary objective was to evaluate the efficacy of Levetiracetam (LEV) dry syrup at doses up to a maximum of 60 mg/kg/day or 3000 mg/day used as an adjunctive therapy in Japanese pediatric subjects aged ≥ 4 to < 16 years and with uncontrolled partial seizures despite treatment with 1 or 2 anti-epileptic drugs (AEDs).

Second Period:

To provide LEV treatment to subjects who were judged by the investigators to benefit from long-term treatment and who are willing to continuously receive this drug and to continuously evaluate the safety of long-term administration of LEV at doses ranging from 20 mg/kg/day or 1000 mg/day to 60 mg/kg/day or 3000 mg/day in subjects who completed the First Period of this study.

Protection of trial subjects:

Not applicable

Background therapy:

One or two anti-epileptic drug(s)

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 29 January 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Japan: 73 |
| Worldwide total number of subjects | 73 |
| 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) | 44 |
| Adolescents (12-17 years) | 29 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Full Analysis Set (FAS) includes all subjects taking at least one dose of study medication. Per-Protocol Set (PPS) is a subset of the FAS, consisting of subjects without major protocol violations affecting the primary efficacy variable.

Pre-assignment

Screening details:

Participant Flow refers to the Full Analysis Set.

First Period started after Baseline (Week 0 to Week 8).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---------------|
| Arm title | Levetiracetam |
|-----------|---------------|

Arm description:

- First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.
- Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.
- Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped.

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

Dosage and administration details:

First Period: Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.

Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.

| | |
|--|-------------------------|
| Investigational medicinal product name | Levetiracetam dry syrup |
| Investigational medicinal product code | ucb L059 |
| Other name | EKeppra |
| Pharmaceutical forms | Powder for syrup |
| Routes of administration | Oral use |

Dosage and administration details:

First Period: Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.

Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.

| Number of subjects in period 1 | Levetiracetam |
|---------------------------------------|---------------|
| Started | 73 |
| Completed | 35 |
| Not completed | 38 |
| AE, serious fatal | 1 |
| Consent withdrawn by subject | 10 |
| AE, non-serious non-fatal | 5 |
| SAE, non-fatal | 1 |
| Lack of efficacy | 20 |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Levetiracetam |
| Reporting group description: | |
| <ul style="list-style-type: none"> •First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks. •Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted. •Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped. | |

| Reporting group values | Levetiracetam | Total | |
|------------------------------------|---------------|-------|--|
| Number of subjects | 73 | 73 | |
| Age Categorical | | | |
| Units: Subjects | | | |
| >=4 - <8 years | 22 | 22 | |
| >=8 - <12 years | 22 | 22 | |
| >=12 - <16 years | 29 | 29 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 10.1 | | |
| standard deviation | ± 3.4 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 32 | 32 | |
| Male | 41 | 41 | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Japan | 73 | 73 | |
| Hospitalization Status | | | |
| Units: Subjects | | | |
| Yes | 0 | 0 | |
| No | 73 | 73 | |
| Body Weight | | | |
| Units: kilogram (kg) | | | |
| arithmetic mean | 32.43 | | |
| standard deviation | ± 13.2 | - | |
| Height | | | |
| Units: centimeter (cm) | | | |
| arithmetic mean | 134.55 | | |
| standard deviation | ± 20.69 | - | |
| Body Mass Index (BMI) | | | |
| Units: kilogram / meter^2 (kg/m^2) | | | |
| arithmetic mean | 17.15 | | |
| standard deviation | ± 2.99 | - | |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Levetiracetam |
| Reporting group description: | |
| <ul style="list-style-type: none">•First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.•Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.•Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped. | |

Primary: Change from Baseline in partial seizure frequency per week over the 14-weeks Treatment Period

| | |
|---|--|
| End point title | Change from Baseline in partial seizure frequency per week over the 14-weeks Treatment Period ^[1] |
| End point description: | |
| The change in partial seizure frequency from Baseline (B) over the Treatment Period (T) is given as a percentage reduction computed as: (B values- T values) / B values x 100. | |
| Positive values in percent reduction mean that the value decreased from Baseline during the first 14-week Period. | |
| Frequency per week of partial seizures = (Total number of partial seizures in a certain Period/number of observation days in the Period) x 7. | |
| Partial seizures can be classified into: | |
| <ul style="list-style-type: none">- Simple partial seizures- Complex partial seizures- Partial seizures evolving to secondarily generalized seizures. | |
| End point type | Primary |

End point timeframe:

From Baseline (Week 0-8) to the 14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22)); Week 0-22

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: The efficacy of LEV in this study was considered positive if the lower limit of the 2-sided 95 % CI of the median percentage reduction in the partial seizure frequency per week was greater than 16.3 %. This was based on the median percentage reduction of the seizure frequency per week in the placebo in N159. Furthermore, a percentage reduction greater than 16.3 % was considered clinically relevant.

Descriptive statistics with 95 % CI of the median percentage reduction were presented.

| | | | | |
|-----------------------------------|------------------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 73 | | | |
| Units: Percent reduction | | | | |
| median (confidence interval 95%) | | | | |
| median (95 % confidence interval) | 43.21 (26.19 to 52.14) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Treatment-Emergent Adverse Events (TEAEs) during the Second Period (up to three years until the time of approval granted)

| | |
|-----------------|---|
| End point title | Incidence of Treatment-Emergent Adverse Events (TEAEs) during the Second Period (up to three years until the time of approval granted) ^[2] |
|-----------------|---|

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with the pharmaceutical product. Incidence of treatment-emergent AEs is reported by the percentage of subjects with at least one treatment-emergent AE.

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

End point timeframe:

During the second Period from Visit 8 (Week 22) to the end of the Follow-up Period (up to three years until the time of approval granted)

Notes:

[2] - 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: There was no statistical analysis for this endpoint in this open-label study.

| | | | | |
|-----------------------------------|-----------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 98.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in partial seizure frequency per week over the 10-week Evaluation Period

| | |
|-----------------|---|
| End point title | Change from Baseline in partial seizure frequency per week over the 10-week Evaluation Period |
|-----------------|---|

End point description:

The change in partial seizure frequency from Baseline (B) over the Evaluation Period (E) is given as a percentage reduction computed as:

$(B \text{ values} - E \text{ values}) / B \text{ values} \times 100$.

Positive values in percent reduction mean that the value decreased from Baseline to the 10-week Evaluation Period.

Frequency per week of partial seizures = (Total number of partial seizures in a certain Period/number of observation days in the Period) x 7.

Partial seizures can be classified into:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline (Week 0-8) to the 10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22) | |

| | | | | |
|-----------------------------------|------------------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 68 | | | |
| Units: Percent reduction | | | | |
| median (confidence interval 95%) | | | | |
| median (95 % confidence interval) | 39.02 (26.67 to 52.07) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Partial seizure frequency per week over the 14-weeks Treatment Period

| | |
|--|---|
| End point title | Partial seizure frequency per week over the 14-weeks Treatment Period |
| End point description: | |
| The seizure frequency per week was calculated as: Frequency per week of partial seizures = (Total number of partial seizures in the Treatment Period/number of days for observation in the Treatment Period) x 7. Partial seizures can be classified into one of the following three groups: | |
| <ul style="list-style-type: none"> - Simple partial seizures - Complex partial seizures - Partial seizures evolving to secondarily generalized seizures. | |
| End point type | Secondary |
| End point timeframe: | |
| 14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22)) | |

| | | | | |
|---------------------------------------|----------------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 73 | | | |
| Units: Seizures per week | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| median (95 % confidence interval) | 3.92 (0.93 to 17.08) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Partial seizure frequency per week over the 10-weeks Evaluation Period

| | |
|-----------------|--|
| End point title | Partial seizure frequency per week over the 10-weeks Evaluation Period |
|-----------------|--|

End point description:

The seizure frequency per week was calculated as:

Frequency per week of partial seizures = (Total number of partial seizures in the Evaluation Period/number of days for observation in the Evaluation Period) x 7.

Partial seizures can be classified into one of the following three groups:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

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

End point timeframe:

10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22)

| | | | | |
|---------------------------------------|---------------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 68 | | | |
| Units: Seizures per week | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| median (95 % confidence interval) | 3.9 (0.86 to 17.26) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of partial seizures 50 % responders over the 14-weeks Treatment Period

| | |
|-----------------|---|
| End point title | Percentage of partial seizures 50 % responders over the 14-weeks Treatment Period |
|-----------------|---|

End point description:

50 % responders are those subjects which have a 50 % or more reduction in the frequency of partial seizures from Baseline to the Treatment Period. The results show the percentage of participants that are 50 % responders.

Partial seizures can be classified into one of the following three groups:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

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

End point timeframe:

14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22))

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 73 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| number (95% confidence interval) | 38.4 (27.2 to 50.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of partial seizures 50 % responders over the 10-weeks Evaluation Period

| | |
|-----------------|--|
| End point title | Percentage of partial seizures 50 % responders over the 10-weeks Evaluation Period |
|-----------------|--|

End point description:

50 % responders are those subjects which have a 50 % or more reduction in the frequency of partial seizures from Baseline to the Evaluation Period. The results show the percentage of participants that are 50 % responders.

Partial seizures can be classified into one of the following three groups:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

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

End point timeframe:

10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22)

| | | | | |
|-----------------------------------|---------------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 68 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| number (95% confidence interval) | 38.2 (26.7 to 50.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seizure-free subjects over the 14-weeks Treatment Period

| | |
|-----------------|--|
| End point title | Number of seizure-free subjects over the 14-weeks Treatment Period |
|-----------------|--|

End point description:

Seizure-free means not having a seizure of type I (Partial seizure).

Partial seizures can be classified into one of the following three groups:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 14-weeks Treatment Period (First Period: 4 weeks Up-titration (Week 8-12) and 10 weeks Evaluation (Week 12-22)) | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 73 | | | |
| Units: participants | | | | |
| participants | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seizure-free subjects over the 10-weeks Evaluation Period

| | |
|-----------------|---|
| End point title | Number of seizure-free subjects over the 10-weeks Evaluation Period |
|-----------------|---|

End point description:

Seizure-free means not having a seizure of type I (Partial seizure).

Partial seizures can be classified into one of the following three groups:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to secondarily generalized seizures.

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

End point timeframe:

10-weeks Evaluation Period (Part of the first Period: Week 12 to Week 22)

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 68 | | | |
| Units: participants | | | | |
| participants | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment-emergent Adverse Drug Reactions (ADRs) during the Second Period (up to three years until the time of approval granted)

| | |
|--|---|
| End point title | Incidence of treatment-emergent Adverse Drug Reactions (ADRs) during the Second Period (up to three years until the time of approval granted) |
| End point description: An Adverse Drug Reaction (ADR) is an Adverse Event for which a causal relationship between the product and the occurrence is suspected. Incidence of ADRs is reported by the number of subjects with at least one ADR. | |
| End point type | Secondary |
| End point timeframe: During the second Period from Visit 8 (Week 22) to the end of the Follow-up Period (up to three years until the time of approval granted) | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55 | | | |
| Units: participants | | | | |
| participants | 15 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in partial seizure frequency per week for the Second Period (up to three years from informed consent until the time of approval granted)

| | |
|---|---|
| End point title | Change from Baseline in partial seizure frequency per week for the Second Period (up to three years from informed consent until the time of approval granted) |
| End point description: The outcome was also calculated for each 3-month Period but here only the result for the total Second Evaluation Period (Second Period without following 6-weeks Withdrawal Period for withdrawers) is presented. Change in partial seizure frequency from Baseline (B) over Second Evaluation Period (E) is given as a percentage reduction computed as: $(B \text{ values} - E \text{ values}) / B \text{ values} \times 100$. Positive values in percent reduction show a decrease from Baseline. Frequency per week of partial seizures = (Total number of partial seizures in a certain Period/number of observation days in the Period) x 7. | |
| End point type | Secondary |
| End point timeframe: From Baseline (Week 0-8) until the time of approval granted (up to three years from date of informed consent (Week 0); without 6-weeks Withdrawal Period) | |

| | | | | |
|---------------------------------------|-----------------------|--|--|--|
| End point values | Levetiracetam | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 55 | | | |
| Units: Percent reduction | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| median (inter-quartile range) | 41.32 (15.37 to 82.4) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected over the whole study from Baseline (Visit 2) over the complete First Period (14 weeks plus up to 6-week Down-titration and Follow-up) and the Second Period (Week 22 to the end of study).

Adverse event reporting additional description:

AEs refer to the Full Analysis Set (FAS). FAS includes all subjects which received at least one dose of study medication.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Levetiracetam |
|-----------------------|---------------|

Reporting group description:

- First Period (4 weeks Up-titration and 10 weeks Evaluation): Dry syrup 50 %, 20 mg/kg/day or 1000 mg/day, 40 mg/kg/day or 2000 mg/day, 60 mg/kg/day or 3000 mg/day, twice daily administration Per Os (PO) for 14 weeks.

- Second Period: Dry syrup 50 % or tablets (250 mg and 500 mg strengths), 20 to 60 mg/kg/day or 1000 to 3000 mg/day, twice daily administration Per Os (PO) until indication granted.

- Withdrawal Period (6 weeks): Patients on the dose at 60 mg/kg/day or 3000 mg/day will be decreased to 40 mg/kg/day or 2000 mg/day for first 2 weeks and then to 20 mg/kg/day or 1000 mg/day for 2 additional weeks. For patients on the dose at 40 mg/kg/day or 2000 mg/day, the dosage will be decreased to 20 mg/kg/day or 1000 mg/day for 2 weeks and then the treatment with LEV will be stopped.

| Serious adverse events | Levetiracetam | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 73 (10.96%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Near drowning | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 2 / 73 (2.74%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Status epilepticus | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Strabismus | | | |
| alternative dictionary used: MedDRA 14.0 | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acetonaemic vomiting | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dental caries | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Conversion disorder | | | |
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 73 (2.74%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 73 (1.37%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Levetiracetam | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 66 / 73 (90.41%) | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 8 / 73 (10.96%) | | |
| occurrences (all) | 11 | | |
| Excoriation | | | |
| subjects affected / exposed | 6 / 73 (8.22%) | | |
| occurrences (all) | 8 | | |
| Wound | | | |
| subjects affected / exposed | 5 / 73 (6.85%) | | |
| occurrences (all) | 10 | | |
| Arthropod bite | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 21 | | |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 34 / 73 (46.58%) | | |
| occurrences (all) | 48 | | |
| Headache | | | |
| subjects affected / exposed | 10 / 73 (13.70%) | | |
| occurrences (all) | 20 | | |
| Convulsion | | | |
| subjects affected / exposed | 7 / 73 (9.59%) | | |
| occurrences (all) | 8 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all) | 17 / 73 (23.29%) 32 4 / 73 (5.48%) 4 | | |
| Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) | 4 / 73 (5.48%) 5 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal Pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dental Caries subjects affected / exposed occurrences (all) | 9 / 73 (12.33%) 16 5 / 73 (6.85%) 5 5 / 73 (6.85%) 7 6 / 73 (8.22%) 7 5 / 73 (6.85%) 11 | | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Rhinitis allergic | 6 / 73 (8.22%) 8 5 / 73 (6.85%) 10 4 / 73 (5.48%) 5 | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 4 / 73 (5.48%) 4 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 6 / 73 (8.22%) | | |
| occurrences (all) | 6 | | |
| Heat rash | | | |
| subjects affected / exposed | 5 / 73 (6.85%) | | |
| occurrences (all) | 5 | | |
| Eczema | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 5 | | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 6 | | |
| Rash | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 6 | | |
| Urticaria | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 4 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 4 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 54 / 73 (73.97%) | | |
| occurrences (all) | 205 | | |
| Influenza | | | |
| subjects affected / exposed | 20 / 73 (27.40%) | | |
| occurrences (all) | 24 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 12 / 73 (16.44%) | | |
| occurrences (all) | 37 | | |
| Gastroenteritis | | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 7 / 73 (9.59%) | | |
| occurrences (all) | 13 | | |
| Impetigo | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 4 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 4 / 73 (5.48%) | | |
| occurrences (all) | 4 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 73 (6.85%) | | |
| occurrences (all) | 5 | | |

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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24018745>