



Clinical trial results:

A Double-blind, Multicenter, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Adjunctive Treatment With Oral Levetiracetam, in Epilepsy Patients Aged 16 Years, With Generalized Tonic-clonic (GTC) Seizures

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-004401-32 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 27 May 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 June 2016 |
| First version publication date | 22 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | N01159 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01228747 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB Japan Co. Ltd. |
| Sponsor organisation address | Shinjuku Grand Tower, 8-17-1, Nishi-shinjuku, Shinjuku-ku, Tokyo, Japan, 160-0023 |
| Public contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 July 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 May 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Levetiracetam treatment used as adjunctive therapy in Japanese and Chinese epilepsy patients aged ≥ 16 years with uncontrolled generalized tonic-clonic seizures despite treatment with 1 or 2 antiepileptic drug(s).

Protection of trial subjects:

Close monitoring of subjects safety status.

Background therapy:

Anti Epileptic Drugs (AED), as indicated and predefined in the protocol, were allowed as oral administration of 1 or 2 stable concomitant AEDs. For sudden aggravation or cluster seizures and if the subject's condition require rescue medication(s) during minor surgical procedures rescue medication was permitted as specified per protocol.

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 21 October 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 | China: 208 |
| Country: Number of subjects enrolled | Japan: 43 |
| Worldwide total number of subjects | 251 |
| 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) | 15 |

| | |
|----------------------|-----|
| Adults (18-64 years) | 234 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in Japan and China in October 2010.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set consisting of all screened subjects who signed the Informed Consent form, participated in the prospective Baseline Period and were randomized at Visit 2.

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, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PL1 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Matching placebo for 28 weeks

Placebo: Matching oral placebo tablets twice daily for 28 weeks

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

Arm description:

Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks
Levetiracetam: Oral dose tablets, twice daily

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Levetiracetam |
| Investigational medicinal product code | PR1 |
| Other name | Keppra |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks
Levetiracetam: Oral dose tablets, twice daily

| Number of subjects in period 1 | Placebo | Levetiracetam |
|---------------------------------------|---------|---------------|
| Started | 125 | 126 |
| Completed | 60 | 81 |
| Not completed | 65 | 45 |
| Adverse event, serious fatal | 3 | - |
| Consent withdrawn by subject | 5 | 1 |
| Serious adverse event, non-fatal | 1 | - |
| Other Reason | 2 | 5 |
| Adverse event, non-serious non-fatal | 4 | 4 |
| Lost to follow-up | 4 | 3 |
| Protocol deviation | 6 | 5 |
| Lack of efficacy | 40 | 27 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks | |
| Reporting group title | Levetiracetam |
| Reporting group description: | |
| Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks | |
| Levetiracetam: Oral dose tablets, twice daily | |

| Reporting group values | Placebo | Levetiracetam | Total |
|-------------------------|---------|---------------|-------|
| Number of subjects | 125 | 126 | 251 |
| Age Categorical | | | |
| Units: Subjects | | | |
| <=18 years | 11 | 10 | 21 |
| Between 18 and 65 years | 113 | 115 | 228 |
| >=65 years | 1 | 1 | 2 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 32.8 | 31.5 | - |
| standard deviation | ± 12.5 | ± 11.3 | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 49 | 47 | 96 |
| Male | 76 | 79 | 155 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| China | 104 | 104 | 208 |
| Japan | 21 | 22 | 43 |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks | |
| Reporting group title | Levetiracetam |
| Reporting group description: | |
| Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks Levetiracetam: Oral dose tablets, twice daily | |
| Subject analysis set title | Levetiracetam Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Full Analysis Set consisted of all subjects in the Safety Set who had an evaluable Baseline and at least 1 post-Baseline GTC seizure count data point for the primary efficacy analysis excluding those who had seriously violated GCP. Evaluable Baseline for the primary efficacy analysis: at least 1 GTC seizure was documented for the Combined Baseline. | |
| Subject analysis set title | Placebo Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Full Analysis Set consisted of all subjects in the Safety Set who had an evaluable Baseline and at least 1 post-Baseline GTC seizure count data point for the primary efficacy analysis excluding those who had seriously violated GCP (Good Clinical Practice). Evaluable Baseline for the primary efficacy analysis: at least 1 GTC seizure was documented for the Combined Baseline. | |

Primary: Percentage change from the Combined Baseline in the generalized tonic-clonic seizure frequency per week over the 28-week Treatment Period (Dose Adjustment + Evaluation Periods)

| | |
|--|--|
| End point title | Percentage change from the Combined Baseline in the generalized tonic-clonic seizure frequency per week over the 28-week Treatment Period (Dose Adjustment + Evaluation Periods) |
| End point description: | |
| Percentage change in generalized tonic-clonic (GTC) seizure frequency per week from Combined Baseline B over the Treatment Period A is calculated using the equation: Percentage change from Baseline = $((A-B)/B)*100$. Percentage change from baseline is not defined for subjects whose baseline information is missing / unknown or equal to zero, or whose seizure frequency per week is missing / unknown. A negative value in change in generalized tonic-clonic (GTC) seizure frequency indicates a reduction of generalized tonic-clonic (GTC) seizure frequency over the 28-week treatment Period. Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline to Week 28 | |

| End point values | Placebo Full Analysis Set | Levetiracetam Full Analysis Set | | |
|--------------------------------------|---------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 109 | 117 | | |
| Units: Percentage Change | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---------|------------------|------------------|--|--|
| Overall | -13.19 (± 55.54) | -68.22 (± 34.95) | | |
|---------|------------------|------------------|--|--|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| The statistical hypotheses, null hypothesis (H0) and alternate hypothesis (H1), are stated below: | |
| H0: $\mu\text{LEV} = \mu\text{PBO}$ vs. H1: $\mu\text{LEV} \neq \mu\text{PBO}$ | |
| ANCOVA on the endpoint "percentage change from Combined Baseline of GTC seizures per week" using "treatment" and "country" as factors (categorical predictors) and "Combined Baseline GTC seizure frequency per week" as a covariate (a continuous predictor) where μLEV and μPBO are adjusted means for LEV and PBO, respectively. | |
| Comparison groups | Placebo Full Analysis Set v Levetiracetam Full Analysis Set |
| Number of subjects included in analysis | 226 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Method | ANCOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | -56.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -68.24 |
| upper limit | -44.02 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.15 |

Secondary: The percentage change in generalized tonic-clonic seizure frequency per week from the Combined Baseline over the Evaluation Period

| | |
|--|--|
| End point title | The percentage change in generalized tonic-clonic seizure frequency per week from the Combined Baseline over the Evaluation Period |
| End point description: | |
| Percentage change in generalized tonic-clonic (GTC) seizure frequency per week from combined baseline B over the Evaluation Period A is calculated using the equation: Percentage change from Baseline = $((A-B)/B)*100$. Percentage change from baseline is not defined for subjects whose baseline Information is missing / unknown or equal to zero, or whose seizure frequency per week is missing / unknown. A negative value in change in generalized tonic-clonic (GTC) seizure frequency indicates a reduction of generalized tonic-clonic (GTC) seizure frequency. Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Evaluation Period (Week 12 to Week 28) | |

| End point values | Placebo Full Analysis Set | Levetiracetam Full Analysis Set | | |
|--------------------------------------|---------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 97 | 108 | | |
| Units: Percentage Change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall | -4.44 (± 153.82) | -68.27 (± 42.63) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Generalized tonic-clonic seizures 50 % responder rate (the proportion of subjects with 50 % or more reduction from the Combined Baseline in the frequency of generalized tonic-clonic seizures) during the Treatment Period

| | |
|-----------------|---|
| End point title | Generalized tonic-clonic seizures 50 % responder rate (the proportion of subjects with 50 % or more reduction from the Combined Baseline in the frequency of generalized tonic-clonic seizures) during the Treatment Period |
|-----------------|---|

End point description:

A subject with an at least 50 % reduction in weekly generalized tonic-clonic (GTC) seizure frequency from Combined Baseline Period to the Treatment Period is considered a GTC 50 % responder.
Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline

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

End point timeframe:

From Baseline to Week 28

| End point values | Placebo Full Analysis Set | Levetiracetam Full Analysis Set | | |
|-----------------------------|---------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 109 | 117 | | |
| Units: participants | | | | |
| Overall | 31 | 91 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Generalized tonic-clonic seizures 50 % responder rate (the proportion of subjects with 50 % or more reduction from the Combined Baseline in the frequency

of generalized tonic-clonic seizures) during the Evaluation Period

| | |
|-----------------|--|
| End point title | Generalized tonic-clonic seizures 50 % responder rate (the proportion of subjects with 50 % or more reduction from the Combined Baseline in the frequency of generalized tonic-clonic seizures) during the Evaluation Period |
|-----------------|--|

End point description:

A subject with an at least 50 % reduction in weekly generalized tonic-clonic (GTC) seizure frequency from Combined Baseline Period to the Evaluation Period is considered a GTC 50 % responder.

Combined Baseline means: a 4-week Retrospective Baseline + 4-week Prospective Baseline or 8-week Prospective Baseline

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

End point timeframe:

From Baseline to Evaluation Period (Week 12 to Week 28)

| End point values | Placebo Full Analysis Set | Levetiracetam Full Analysis Set | | |
|-----------------------------|---------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 97 | 108 | | |
| Units: participants | | | | |
| Overall | 33 | 82 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Generalized tonic-clonic seizure freedom over the Evaluation Period

| | |
|-----------------|---|
| End point title | Generalized tonic-clonic seizure freedom over the Evaluation Period |
|-----------------|---|

End point description:

A subject with a non-missing weekly generalized tonic-clonic (GTC) baseline seizure frequency and a weekly GTC seizure frequency of zero throughout the Evaluation Period, is considered as a GTC seizure-free subject on the Evaluation Period.

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

End point timeframe:

Evaluation Period (Week 12 to Week 28)

| End point values | Placebo Full Analysis Set | Levetiracetam Full Analysis Set | | |
|-----------------------------|---------------------------|---------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 97 | 108 | | |
| Units: participants | | | | |
| Overall | 3 | 32 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from the Prospective Baseline Period (Week -8 to Week 0) over Dose Adjustment (12 weeks) and Evaluation Period (16 weeks) until Conversion or Withdrawal Period (4-6 weeks).

Adverse event reporting additional description:

Adverse Events refer to the Safety Set (SS), which is a subset of the Randomized Set and consisted of all subjects who received at least 1 dose of study medication after randomization, either Placebo or Levetiracetam.

Adverse Events were presented for the Dose Adjustment and Evaluation Period.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17 |

Reporting groups

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

Reporting group description:

Levetiracetam treatment with dosing of 1000 mg/day or 2000 mg/day or 3000 mg/day for 28 weeks
Levetiracetam: Oral dose tablets, twice daily

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching placebo for 28 weeks Placebo: Matching oral placebo tablets twice daily for 28 weeks

| Serious adverse events | Levetiracetam | Placebo | |
|--|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 4 / 125 (3.20%) | |
| number of deaths (all causes) | 0 | 3 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Drowning | | | |
| subjects affected / exposed | 0 / 126 (0.00%) | 2 / 125 (1.60%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Sudden unexplained death in epilepsy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 126 (0.00%) | 1 / 125 (0.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 126 (0.79%) | 0 / 125 (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 | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 126 (31.75%) | 32 / 125 (25.60%) | |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 7 / 126 (5.56%) | 4 / 125 (3.20%) | |
| occurrences (all) | 8 | 4 | |
| Protein urine present | | | |
| subjects affected / exposed | 10 / 126 (7.94%) | 1 / 125 (0.80%) | |
| occurrences (all) | 11 | 1 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 126 (3.17%) | 9 / 125 (7.20%) | |
| occurrences (all) | 7 | 14 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 126 (5.56%) | 5 / 125 (4.00%) | |
| occurrences (all) | 8 | 5 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 24 / 126 (19.05%) | 20 / 125 (16.00%) | |
| occurrences (all) | 33 | 36 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 30 July 2010 | The substantial Protocol Amendment 1 provided the following major changes: <ul style="list-style-type: none">• To detect pregnancy, the sample utilized for the test to detect the level of beta human chorionic gonadotropin (β-hCG) was changed to blood from urine due to issues found in preparation for the central measurements that led to an increase in the volume of the blood sample.• UCB changed the number of the categories for causal relationship of AEs to the study medication from 4 to 2 ("related" or "not related").• UCB changed the standard module of the eCRF; because of this change, 'laboratory abnormalities that the investigator judges clinically relevant' no longer needed to be recorded in the eCRF.• LEV was granted regulatory approval in Japan after the final protocol was approved. |
| 27 October 2011 | The substantial Protocol Amendment 2 provided the following change: the use of commercial Keppra in the Named Patient Program for subjects in China who completed N01159 was clarified. Changes to the previous amendment were required for clarification. |
| 16 February 2012 | The substantial Protocol Amendment 3 provided the following changes: the study duration was extended (originally planned from the fourth quarter of 2010 to the first quarter of 2013, extended to the fourth quarter of 2013) and the visit window during the Baseline Period was clarified. Ilepcimide was included in the list of permitted concomitant AEDs. |
| 03 September 2012 | The substantial Protocol Amendment 4 provided the following change: the required sample size in Japan was changed based on the progress assessment of the recruitment of the Japanese subjects (originally, 78 subjects were planned for Japan [and 154 subjects in China] and this was changed to 26 subjects in Japan [and 206 subjects in China]). In addition, the study duration was extended to the second quarter of 2014. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported