



Clinical trial results:

An open-label, multicenter, follow-up study to evaluate the safety and efficacy of levetiracetam (LEV) (oral tablets of 166, 250 or 500 mg b.i.d.), at individualized doses up to a maximum of 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg), in children (4 years old), adolescents and adults suffering from primary generalized seizures

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2004-001997-13 |
| Trial protocol | AT EE |
| Global end of trial date | 10 July 2007 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 June 2016 |
| First version publication date | 11 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|------|
| Sponsor protocol code | N167 |
|-----------------------|------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00150748 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB Pharma SA |
| Sponsor organisation address | Chemin du Foriest, Braine l'Alleud, Belgium, B - 1420 |
| 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 | 14 March 2008 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 July 2007 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of N167 was to evaluate the safety and efficacy of LEV at individualized doses with a maximum dose of 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg), in reducing seizures in children, adolescents, and adults suffering from Primary generalized (type II) seizures.

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

| | |
|---|------------------|
| Actual start date of recruitment | 01 November 2001 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 7 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Canada: 38 |
| Country: Number of subjects enrolled | Estonia: 5 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Ireland: 2 |
| Country: Number of subjects enrolled | Italy: 7 |
| Country: Number of subjects enrolled | Mexico: 46 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | Poland: 41 |
| Country: Number of subjects enrolled | Russian Federation: 21 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 13 |
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects | 237 |
| EEA total number of subjects | 103 |

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) | 10 |
| Adolescents (12-17 years) | 23 |
| Adults (18-64 years) | 204 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in November 2001. 217 subjects were enrolled from studies N01057 and N166, which are defined as the ITT Population, and 20 subjects were enrolled from studies N129 and N164.

Pre-assignment

Screening details:

Participant Flow shows all enrolled subjects.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Levetiracetam (subjects from N01057 and N166) |

Arm description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

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

Dosage and administration details:

All subjects received open-label Levetiracetam during this study. Investigational product consisted of film-coated tablets of 166, 250, or 500 mg Levetiracetam to be taken orally with or without food.

| | |
|------------------|---|
| Arm title | Levetiracetam (subjects from N129 and N164) |
|------------------|---|

Arm description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

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

Dosage and administration details:

All subjects received open-label Levetiracetam during this study. Investigational product consisted of film-coated tablets of 166, 250, or 500 mg Levetiracetam to be taken orally with or without food.

| Number of subjects in period 1 | Levetiracetam (subjects from N01057 and N166) | Levetiracetam (subjects from N129 and N164) |
|---------------------------------------|---|---|
| Started | 217 | 20 |
| Completed | 125 | 3 |
| Not completed | 92 | 17 |
| AE, serious fatal | 1 | - |
| Consent withdrawn by subject | 11 | 3 |
| Loss of efficacy | 2 | - |
| Other Reason | 20 | 11 |
| AE, non-serious non-fatal | 9 | - |
| Lost to follow-up | 10 | 2 |
| SAE, non-fatal | 10 | - |
| Lack of efficacy | 26 | - |
| Protocol deviation | 3 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Levetiracetam (subjects from N01057 and N166) |
|-----------------------|---|

Reporting group description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

| | |
|-----------------------|---|
| Reporting group title | Levetiracetam (subjects from N129 and N164) |
|-----------------------|---|

Reporting group description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

| Reporting group values | Levetiracetam (subjects from N01057 and N166) | Levetiracetam (subjects from N129 and N164) | Total |
|---------------------------------------|---|---|-------|
| Number of subjects | 217 | 20 | 237 |
| Age Categorical Units: Subjects | | | |
| Children (2-11 years) | 7 | 3 | 10 |
| Adolescents (12-17 years) | 23 | 0 | 23 |
| Adults (18-64 years) | 187 | 17 | 204 |
| Age Continuous Units: years | | | |
| arithmetic mean | 27.99 | 31.1 | |
| standard deviation | ± 10.88 | ± 12.28 | - |
| Gender Categorical Units: Subjects | | | |
| Male | 91 | 9 | 100 |
| Female | 126 | 11 | 137 |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | Levetiracetam (subjects from N01057 and N166) |
|-----------------------|---|

Reporting group description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

| | |
|-----------------------|---|
| Reporting group title | Levetiracetam (subjects from N129 and N164) |
|-----------------------|---|

Reporting group description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

| | |
|----------------------------|--------------------------------------|
| Subject analysis set title | All intent-to-treat (ITT) population |
|----------------------------|--------------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The All intent-to-treat (ITT) Population was defined as all subjects coming from study N01057 or N166 who had recorded intake of at least 1 dose of N167 study medication.

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Tonic-Clonic subpopulation |
|----------------------------|----------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Any N166/N01057 ITT subject with a Tonic-Clonic seizure frequency per week >0 at N166 (prospective) or N01057 (combined) Baseline.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Myoclonic subpopulation |
|----------------------------|-------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Any N166/N01057 ITT subject with Myoclonic seizure days per week >0 at N166 (prospective) or N01057 (combined) Baseline.

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Absence subpopulation |
|----------------------------|-----------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Any N166/N01057 ITT subject with a IIA seizure days per week >0 at N166 (prospective) or N01057 (combined) Baseline.

Primary: Number of subjects having at least 6 months of seizure freedom at any time during the Evaluation Period

| | |
|-----------------|--|
| End point title | Number of subjects having at least 6 months of seizure freedom at any time during the Evaluation Period ^[1] |
|-----------------|--|

End point description:

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

End point timeframe:

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: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

| End point values | Levetiracetam (subjects from N01057 and N166) | Levetiracetam (subjects from N129 and N164) | | |
|-----------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 217 | 20 | | |
| Units: Subjects | | | | |
| Number of subjects | 122 | 12 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects having at least 6 months of seizure freedom at any time during the Evaluation Period

| | |
|-----------------|--|
| End point title | Percentage of subjects having at least 6 months of seizure freedom at any time during the Evaluation Period ^[2] |
|-----------------|--|

End point description:

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

End point timeframe:

Evaluation Period

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: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

| End point values | Levetiracetam (subjects from N01057 and N166) | Levetiracetam (subjects from N129 and N164) | | |
|-------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 217 | 20 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| percentage of subjects | 56.2 | 60 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects remaining seizure-free, for the All intent-to-treat (ITT) population, and Tonic-Clonic, Myoclonic, and Absence subpopulations since the beginning of this study N167 (Visit 1) during the Evaluation Period

| | |
|-----------------|--|
| End point title | Number of subjects remaining seizure-free, for the All intent-to-treat (ITT) population, and Tonic-Clonic, Myoclonic, and Absence subpopulations since the beginning of this study N167 (Visit 1) during the Evaluation Period |
|-----------------|--|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Visit 1 to the end of the Evaluation Period | |

| End point values | All intent-to-treat (ITT) population | Tonic-Clonic subpopulation | Myoclonic subpopulation | Absence subpopulation |
|---------------------------------|--------------------------------------|----------------------------|-------------------------|-----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 217 | 152 | 121 | 70 |
| Units: Subjects | | | | |
| Number of seizure-free subjects | 49 | 42 | 33 | 24 |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects remaining seizure-free, for the All intent-to-treat (ITT) population, and Tonic-Clonic, Myoclonic, and Absence subpopulations since the beginning of this study N167 (Visit 1) during the Evaluation Period

| | |
|-----------------|--|
| End point title | Percentage of subjects remaining seizure-free, for the All intent-to-treat (ITT) population, and Tonic-Clonic, Myoclonic, and Absence subpopulations since the beginning of this study N167 (Visit 1) during the Evaluation Period |
|-----------------|--|

End point description:

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Visit 1 to the end of the Evaluation Period | |

| End point values | All intent-to-treat (ITT) population | Tonic-Clonic subpopulation | Myoclonic subpopulation | Absence subpopulation |
|-------------------------------------|--------------------------------------|----------------------------|-------------------------|-----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 217 | 152 | 121 | 70 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Percentage of seizure-free subjects | 22.6 | 27.6 | 27.3 | 34.3 |

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction from N01057 or N166 Baseline to the Evaluation Period in seizure frequency per week for Tonic-Clonic subpopulation seizures types

| | |
|------------------------|---|
| End point title | Reduction from N01057 or N166 Baseline to the Evaluation Period in seizure frequency per week for Tonic-Clonic subpopulation seizures types |
| End point description: | A positive value for Reduction of seizure frequency indicates an improvement from Baseline. |
| End point type | Secondary |
| End point timeframe: | From N01057 or N166 Baseline to the Evaluation Period |

| | | | | |
|---------------------------------------|----------------------------|--|--|--|
| End point values | Tonic-Clonic subpopulation | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 152 | | | |
| Units: Reduction of Seizure Frequency | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 0.8 (\pm 1.51) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage reduction from N01057 or N166 Baseline to the Evaluation Period in seizure frequency per week for Tonic-Clonic subpopulation seizures types

| | |
|------------------------|--|
| End point title | Percentage reduction from N01057 or N166 Baseline to the Evaluation Period in seizure frequency per week for Tonic-Clonic subpopulation seizures types |
| End point description: | A positive value for Percentage reduction of seizure frequency indicates an improvement from Baseline. |
| End point type | Secondary |
| End point timeframe: | From N01057 or N166 Baseline to the Evaluation Period |

| | | | | |
|--|----------------------------|--|--|--|
| End point values | Tonic-Clonic subpopulation | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 152 | | | |
| Units: Percentage of Seizure Frequency | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 66.84 (\pm 88.31) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction from N01057 or N166 Baseline to the Evaluation Period in seizure days per week for the ITT population, and Absence and Myoclonic subpopulations

| | |
|-----------------|---|
| End point title | Reduction from N01057 or N166 Baseline to the Evaluation Period in seizure days per week for the ITT population, and Absence and Myoclonic subpopulations |
|-----------------|---|

End point description:

A positive value for Reduction of seizure days per week indicates an improvement from Baseline.

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

End point timeframe:

From N01057 or N166 Baseline to the Evaluation Period

| End point values | All intent-to-treat (ITT) population | Myoclonic subpopulation | Absence subpopulation | |
|--------------------------------------|--------------------------------------|-------------------------|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 217 | 121 | 70 | |
| Units: Reduction of Seizure Days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 1.44 (± 1.69) | 1.48 (± 1.69) | 1.31 (± 2.24) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage reduction from N01057 or N166 Baseline to the Evaluation Period in seizure days per week for the ITT population, and Absence and Myoclonic subpopulations

| | |
|-----------------|--|
| End point title | Percentage reduction from N01057 or N166 Baseline to the Evaluation Period in seizure days per week for the ITT population, and Absence and Myoclonic subpopulations |
|-----------------|--|

End point description:

A positive value for Percentage reduction of seizure days per week indicates an improvement from Baseline.

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

End point timeframe:

From N01057 or N166 Baseline to the Evaluation Period

| End point values | All intent-to-treat (ITT) population | Myoclonic subpopulation | Absence subpopulation | |
|---|--------------------------------------|-------------------------|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 217 | 121 | 70 | |
| Units: Percentage reduction of Seizure Days | | | | |
| arithmetic mean (standard deviation) | | | | |
| arithmetic mean (standard deviation) | 73.06 (± 39.62) | 71.67 (± 70.58) | 60.13 (± 72.26) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Categorical percentage reduction from Baseline to the Evaluation Period in seizure days per week for the ITT population, and Absence and Myoclonic subpopulations

| | |
|------------------------|---|
| End point title | Categorical percentage reduction from Baseline to the Evaluation Period in seizure days per week for the ITT population, and Absence and Myoclonic subpopulations |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Evaluation Period | |

| End point values | All intent-to-treat (ITT) population | Myoclonic subpopulation | Absence subpopulation | |
|-----------------------------|--------------------------------------|-------------------------|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 217 | 121 | 70 | |
| Units: Subjects | | | | |
| < -25 % | 8 | 6 | 8 | |
| -25 % to < 25 % | 12 | 6 | 3 | |
| 25 % to < 50 % | 24 | 7 | 6 | |
| 50 % to < 75 % | 32 | 13 | 6 | |
| 75 % to < 100 % | 89 | 51 | 18 | |
| 100 % | 52 | 38 | 29 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Categorical percentage reduction from Baseline to the Evaluation Period in seizure frequency per week for Tonic-Clonic subpopulation seizures types

| | |
|-----------------|---|
| End point title | Categorical percentage reduction from Baseline to the |
|-----------------|---|

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Visit 1 (Week 0) until the end of study (up to 1764 days).

Adverse event reporting additional description:

Adverse Events refer to the Intent-to-Treat (ITT) Population, including all subjects who had recorded intake of at least 1 dose of N167 study drug.

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

Dictionary used

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

| | |
|--------------------|-----|
| Dictionary version | 7.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Levetiracetam (subjects from N01057 and N166) |
|-----------------------|---|

Reporting group description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

| | |
|-----------------------|---|
| Reporting group title | Levetiracetam (subjects from N129 and N164) |
|-----------------------|---|

Reporting group description:

Subjects received treatment up to 1764 days during the Evaluation Period. Up to 4000 mg/day (or 80 mg/kg/day for children and adolescents less than 50 kg). Oral tablets of 166, 250, or 500 mg Levetiracetam twice daily (b.i.d.).

| Serious adverse events | Levetiracetam (subjects from N01057 and N166) | Levetiracetam (subjects from N129 and N164) | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 31 / 217 (14.29%) | 4 / 20 (20.00%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye injury | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scapula fracture | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 7 / 217 (3.23%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (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 | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postictal state | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal | | | |

| | | | |
|--|-----------------|----------------|--|
| conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 4 / 217 (1.84%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Unintended pregnancy | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abortion | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-uterine death | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Premature baby | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 20 (5.00%) | |
| 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 | | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Ulcer | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash erythematous | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Schizophrenia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Suicidal ideation | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scoliosis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implant site infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Levetiracetam (subjects from N01057 and N166) | Levetiracetam (subjects from N129 and N164) | |
|--|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 106 / 217 (48.85%) | 16 / 20 (80.00%) | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 17 / 217 (7.83%) | 2 / 20 (10.00%) | |
| occurrences (all) | 17 | 2 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-------------------------|----------------------|--|
| Contusion subjects affected / exposed occurrences (all) | 0 / 217 (0.00%) 0 | 2 / 20 (10.00%) 2 | |
| Nervous system disorders Convulsion subjects affected / exposed occurrences (all) | 0 / 217 (0.00%) 0 | 5 / 20 (25.00%) 5 | |
| Headache subjects affected / exposed occurrences (all) | 40 / 217 (18.43%) 93 | 2 / 20 (10.00%) 5 | |
| Tremor subjects affected / exposed occurrences (all) | 15 / 217 (6.91%) 17 | 0 / 20 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 18 / 217 (8.29%) 25 | 2 / 20 (10.00%) 2 | |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 13 / 217 (5.99%) 15 | 0 / 20 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 217 (0.00%) 0 | 2 / 20 (10.00%) 4 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 217 (0.00%) 0 | 3 / 20 (15.00%) 6 | |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 0 / 217 (0.00%) 0 | 2 / 20 (10.00%) 2 | |
| Respiratory, thoracic and mediastinal disorders Sinus pain subjects affected / exposed occurrences (all) | 0 / 217 (0.00%) 0 | 2 / 20 (10.00%) 2 | |
| Psychiatric disorders | | | |

| | | | |
|---|-------------------|-----------------|--|
| Depression | | | |
| subjects affected / exposed | 15 / 217 (6.91%) | 0 / 20 (0.00%) | |
| occurrences (all) | 16 | 0 | |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Stress symptoms | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 20 / 217 (9.22%) | 2 / 20 (10.00%) | |
| occurrences (all) | 30 | 2 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 24 / 217 (11.06%) | 2 / 20 (10.00%) | |
| occurrences (all) | 43 | 2 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 3 / 20 (15.00%) | |
| occurrences (all) | 0 | 3 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 13 / 217 (5.99%) | 2 / 20 (10.00%) | |
| occurrences (all) | 16 | 3 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 3 / 20 (15.00%) | |
| occurrences (all) | 0 | 5 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 217 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 08 September 2003 | <p>The core protocol amendment was issued on 08 Sep 2003 and concerned the following:</p> <ul style="list-style-type: none">• The number of participating sites and countries was extended due to a delay in recruitment in the prior N166 and N01057 studies.• Adverse events reported in postmarketing experience were added to protocol Section 2.2.4, Adverse Events in Clinical Studies (Section 16.1.1).• Some administrative changes were made to the protocol that did not alter the conduct of the study (eg, emergency contacts were updated and various edits made to sentences for clarification only). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported