UCB reference No.: RXCE06E1682

Approved by UCB 18-Mar-2008

# Clinical Study Summary (CSS)

DEV/SGE/03853.2007

**CT Registry ID#: NCT00615615**
**Study No.: N159**

*These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.*

Based on Clinical Study Report document reference code: RRCE04E2401

| **Proprietary Drug Name** | **INN** | **Therapeutic area and indication(s)** |
|---|---|---|
| Keppra® Tablets | Levetiracetam | Epilepsy |

**Name of Sponsor/Company:** UCB Pharma SA

**Title of Study:**
Evaluation of the efficacy and tolerability of levetiracetam add-on treatment in refractory pediatric patients with partial onset seizures: a 28-week double-blind, placebo-controlled multi-center trial

**Investigator(s) (number only):** 64

**Study Center(s) (number only):** 60

**Length of Study:**
Date first patient enrolled: 20-Sep-1999
Date last patient completed: 03-Mar-2003

Phase of Development: Phase III

**Abstract:**
The objective of this study was to evaluate the efficacy and safety of a levetiracetam (LEV) dosage level up to 60 mg/kg/day used as adjunctive therapy in the treatment of children (4-16 years) with refractory partial onset seizures. The primary efficacy parameter was the partial onset (Type I, Type IC included) seizure frequency per week during the Treatment Period. Safety assessments included monitoring of adverse events (AE), safety laboratory tests, LEV and AED plasma levels, physical and neurological examinations, vital signs, body weight, and electrocardiograms (ECGs). Subjects were to be 4-16 years old, had a diagnosis of epilepsy (≥ 6 months prior to the Selection Visit) with uncontrolled partial onset seizures, whether or not secondarily generalized, had an antiepileptic drug (AED) therapy (≤ 2 AEDs) which was unsatisfactory in terms of efficacy or safety as considered by the Investigator, and had experienced ≥ 4 partial onset seizures in the 4 weeks prior to screening, as well as ≥ 4 partial onset seizures in each of the 4-week periods during Baseline. The trial consisted of a selection visit, an 8-week baseline period, a 14-week treatment period with LEV or placebo (PBO) (three 2-week fixed dose titration intervals, followed by an additional 8 weeks at the maximum tolerated dose), and a 6-week withdrawal period, for a maximum of 28 weeks of study participation. Subjects who chose to continue open-label LEV treatment in the follow-up study, did no go through the withdrawal period. Analysis were performed on the Intent-to-Treat population which included all randomized subjects who took at least one dose of study medication, except 16 subjects randomized at site 55 were excluded due to unreliability of the data. The primary efficacy analysis was the comparison of POS seizure frequency per week over the treatment period between the treatment groups through an ANCOVA model. The model was applied on $\log_e$ (x+1) transformed seizure frequency, including treatment as a factor and $\log_e$ (x+1) transformed baseline seizure frequency per week as a covariate. The difference in treatment LSmeans with a 2-sided 95% confidence interval (CI) was computed and expressed as a percent reduction over PBO (=100 x (1 - exp(LSmean LEV – LSmean PBO))).

| **CT Registry ID#: NCT00615615**<br>**Study No.: N159** | | |
|---|---|---|
| **Number of Subjects:** | **PBO** | **LEV** |
| Planned, N: | 97 | 97 |
| Randomized, N: | 107 | 109 |
| Intent-To-Treat population[(a)], N | 97 | 101 |
| Completed, n (%): | 83 (85.6) | 94 (93.1) |
| Number of Subjects Withdrawn, n (%): | 14 (14.4) | 7 (6.9) |
| Withdrawn due to Adverse Events, n (%): | 9 (9.3) | 5 (5.0) |
| Withdrawn for Other Reasons, n (%): | 5 (5.2) | 2 (2.0) |
| [(a)]All 16 subjects at Site 55 were excluded due to unreliable data and 2 subjects discontinued prior to study drug intake. | | |
| **Demography:** | **PBO (N=97)** | **LEV (N=101)** |
| Gender (Females/Males): | 51/46 | 47/54 |
| Age (years), mean (SD): | 9.80 (3.43) | 10.23 (3.23) |
| Race, n (%): | | |
| White/Caucasian | 65 (67.0) | 74 (73.3) |
| Hispanic | 11 (11.3) | 9 (8.9) |
| Black/African-American | 12 (12.4) | 13 (12.9) |
| Asian/Pacific Islander | 1 (1.0) | 2 (2.0) |
| Indian/Pakistani | 0 | 1 (1.0) |
| American Indian/Alaskan Native | 2 (2.1) | 0 |
| Other/Mixed race | 6 (6.2) | 2 (2.0) |

**Safety Outcomes:**

**- Summary of treatment emergent adverse events, deaths, other serious adverse events and certain other significant adverse events:**

Overall, 88.1% and 91.8% subjects of the LEV and PBO group respectively reported treatment-emergent (TE) AEs during the trial. The most commonly reported TEAEs in the LEV and PBO groups were body as whole disorders (58.4% and 64.9% of the subjects, respectively), nervous system disorders (58.4% and 47.4% of the subjects, respectively), and digestive system disorders (36.6% and 38.1% of the subjects, respectively). TEAE considered to be related to the study drug by the Investigator were reported for 55.4% and 40.2% of the subjects in the LEV and PBO group, respectively.

There were no deaths in this trial. Serious AEs (SAEs) were reported for 7.9% and 9.3% subjects in the LEV and PBO groups, respectively. None were considered at least possibly related to the study drug other than 1 case of convulsion in a PBO randomized subject. Five (5.0%) and 9 (9.3%) subjects discontinued the trial due to an AE in the LEV and PBO group, respectively.

No clinically relevant changes were observed for laboratory parameters, vital signs or ECG parameters.

| **Treatment Emergent AEs (TEAE):** | **PBO (N=97)** | **LEV (N=101)** |
|---|---|---|
| Subjects with at least one TEAE, n (%): | 89 (91.8) | 89 (88.1) |
| *COSTART Body System with an incidence of ≥ 15%* | *n (%) [n considered drug-related by the Investigator]* | |
| Body as a whole | 63 (64.9) [10] | 59 (58.4) [17] |
| Nervous system | 46 (47.4) [25] | 59 (58.4) [41] |
| Digestive system | 37 (38.1) [17] | 37 (36.6) [15] |
| Respiratory system | 28 (28.9) [3] | 31 (30.0) [3] |
| **Death and Other SAEs:** | **PBO (N=97)** | **LEV (N=101)** |
| Deaths, n (%): | 0 | 0 |
| Subjects with SAEs, n (%): | 9 (9.3) | 8 (7.9) |
| *COSTART Body System with an incidence of > 2%* | *n (%) [n considered drug-related by the Investigator]* | |
| Nervous system | 5 (5.2) [1] | 4 (4.0) [0] |
| Respiratory system | 4 (4.1) [0] | 0 |
| Procedure | 2 (2.1) [0] | 0 |

| | | |
|---|---|---|
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| **Primary Outcomes:**<br>LEV provided a clinically significant reduction over PBO during the treatment period in partial onset seizure frequency per week that was highly statistically significant (26.8% [95% CI; 14.0%, 37.6%], p=0.0002). | | |
| **Baseline partial onset seizure frequency** | **PBO (N=97)** | **LEV (N=101)** |
| Mean (SD) | 18.46 (50.91) | 19.55 (71.65) |
| Q1-Q3 | 2.5-14.1 | 2.6-12.2 |
| **Treatment partial onset seizure frequency** | **PBO (N=97)** | **LEV (N=101)** |
| Mean (SD) | 12.52 (20.39) | 12.06 (40.17) |
| Q1-Q3 | 1.8-13.9 | 1.0-9.1 |
| Percent reduction over PBO [95% CI] | 26.8 [14.0, 37.6] | |
| p-value | 0.0002 | |
| **Publication Reference(s) based on the study:** Glauser et al. – Neurology 2006; 66: 1654-1660; Jensen et al. – Nat. Clin. Pract. Neurol. 2006; 2: 596-597 | | |
| **Date of report:** 18-Mar-2008 | | |