UCB reference No.: RXCE07J1202

Approved by UCB 01-JUL-2008

Clinical Study Summary (CSS)

CT Registry ID#: NCT00175890
Study No.: N01009

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: RRCE06D1013

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Keppra® Oral Solution	Levetiracetam	Refractory partial onset seizures

Name of sponsor/company: UCB Inc.

Title of study:
A double-blind, randomized, multicenter, placebo-controlled, in-patient, maximum 34-Day study of levetiracetam oral solution (20 to 50mg/kg/d) as adjunctive treatment of refractory partial onset seizures in pediatric epileptic subjects ranging in age from 1 month to less than 4 years of age

Investigator(s) (number only): 81 participated and 62 screened and randomized subjects

Study center(s) (number only): 81 participated and 62 screened and randomized subjects

Length of study:	~34 days	**Phase of development:**
Date first patient enrolled:	15 Oct 2004	Therapeutic confirmatory Phase III
Date last patient completed:	26 Jan 2007	

Abstract:

The objective of this study was to evaluate the efficacy and safety of levetiracetam (LEV) used as adjunctive treatment in pediatric subjects 1 month to less than 4 years of age with refractory partial onset seizures using video electroencephalogram (EEG) as a reliable and objective measurement.

Main inclusion criteria:

- Pediatric subjects from 1 month to less than 4 years of age.
- Pediatric subjects diagnosed with refractory partial onset seizures, on a stable regimen of 1 to 2 other anti-epileptic drugs, and had experienced at least 2 partial onset seizures per week in the 2 weeks prior to screening.
- Patients must have had at least 2 partial onset seizures during the 48-hour video EEG at screening.
- No additions of new AEDs or deletions of current AEDs observed for at least 2 weeks prior to Screening.

Main exclusion criteria:

- A ketogenic diet.
- Previous exposure to LEV.
- Subject with a history of status epilepticus requiring hospitalization during the 1 month prior to Day -8, except for status epilepticus occurring during the first 10 days of life.
- Treatable seizure etiology.
- Current diagnosis of Lennox-Gastaut Syndrome or epilepsy secondary to a progressing cerebral disease.

The study consisted of 4 periods, Selection, Evaluation, Down-titration, and Post-treatment Follow-Up. The Selection Period of up to 9 days included a 48-hour in-patient video EEG. The Evaluation Period of approximately 5 days included a 1-day rapid up-titration to 40 or 50mg/kg/d of LEV or placebo and included a 48-hour in-patient video EEG monitoring at the end of the Evaluation period. The Down Titration Period consisted of 14 days and the Post-Treatment Follow-Up period consisted of up to 4 ± 1 day for subjects not participating in the long-term follow-up study. Dosing was determined by age and weight as follows: children 1 month to less than 6 months old received a dose of 20mg/kg/d titrating to 40mg/kg/d, and children 6 months to less than 4 years old received a dose of 25mg/kg/d titrating to 50mg/kg/d.

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Number of patients:	**Placebo (PBO)**	**LEV**	**Overall**
Planned, N:	55	55	110
Randomized, N:	56	60	116
mTT Population	51	58	109
Completed, n (%):	53 (94.6)	58 (96.7)	111 (95.7)
Withdrawn, n (%):	3 (5.4)	2 (3.3)	5 (4.3)
Withdrawn due to adverse events, n (%):	1 (1.8)	2 (3.3)	3 (2.6)
Withdrawn due to protocol violation, n (%):	1 (1.8)	0	1 (0.9)
Withdrawal of consent, n (%)	1 (1.8)	0	1 (0.9)
Demography:			
Gender (females/males):	29/27	30/30	59/57
Age (months), mean (SD):	23.46 (12.06)	23.40 (13.43)	23.43 (12.73)
Race, n (%):			
Caucasian	39 (69.6)	54 (90.0)	93 (80.2)
American Indian/Alaskan	2 (3.6)	4 (6.7)	6 (5.2)
Other/Mixed race	8 (14.3)	2 (3.3)	10 (8.6)
Black	6 (10.7)	0	6 (5.2)
Asian	1 (1.8)	0	1 (0.9)
Ethnicity, n (%):			
Hispanic or Latino	16 (28.6)	22 (36.7)	38 (32.8)
Not Hispanic or not Latino	40 (71.4)	38 (63.3)	78 (67.2)
Weight (kg), mean (SD):	11.74 (4.05)	11.17 (3.63)	11.45 (3.83)
Height (cm), mean (SD):	82.73 (12.90)	84.02 (13.07)	83.41 (12.95)
Body Mass Index (kg/m^2), mean (SD):	16.37 (2.63)	15.51 (2.12)	15.91 (2.40)
Body Surface Area (m^2), mean (SD):	0.093 (0.076)	0.089 (0.075)	0.091 (0.075)

Safety outcomes:

The proportion of subjects experiencing at least 1 treatment-emergent adverse event (TEAE) was 55% in the LEV group compared with 44.6% in the PBO group. The most frequently reported TEAEs in the LEV-treated group were somnolence and irritability. Somnolence was reported in 8 subjects (13.3%) in the LEV group and 1 subject (1.8%) in the PBO group; irritability was reported in 7 subjects (11.7%) in the LEV group with no incidence in the PBO group. The incidences of other AEs were similar in both groups. The proportion of subjects with treatment-related adverse events (AEs) was 21.7% in the LEV group compared with 7.1% in the PBO group. Two subjects permanently discontinued treatment with LEV (due to severe food aversion and moderate intermittent convulsions) and 1 subject temporarily discontinued treatment with LEV due to an AE (mild rash). One serious adverse event (SAE) was reported in each treatment group (pyrexia in the LEV group and urinary tract infection in the PBO group), neither was considered treatment-related. There were no deaths during the study; and no clinically relevant changes from baseline were observed in the hematology and blood chemistry parameters. The overall results are consistent with the known safety profile for LEV.

Safety results	PBO (N=56)	LEV (N=60)
Total number of TEAEs	47	65
Subjects with at least 1 TEAE, n(%)	25 (44.6)	33 (55.0)
Subjects with at least 1 TEAE by UCB system organ class (SOC)	**n(%) [n considered drug-related by the investigator]**	
Blood and lymphatic system disorders	0	1 (1.7) [0]
Ear and labyrinth disorders	1 (1.8) [0]	2 (3.3) [0]
Gastrointestinal disorders	6 (10.7) [0]	5 (8.3) [0]
General disorders and administration site conditions	4 (7.1) [0]	5 (8.3) [2]
Hepatobiliary disorders	0	1 (1.7) [1]
Infections and infestations	10 (17.9) [0]	8 (13.3) [0]
Injury, poisoning and procedural complications	1 (1.8) [0]	3 (5.0) [0]
Metabolism and nutrition disorders	0	3 (5.0) [1]
Nervous system disorders	2 (3.6) [2]	13 (21.7) [7]
Psychiatric disorders	3 (5.4) [2]	10 (16.7) [4]
Reproductive system and breast disorders	0	1 (1.7) [0]
Respiratory, thoracic and mediastinal disorders	4 (7.1) [0]	2 (3.3) [0]
Skin and subcutaneous tissue disorders	5 (8.9) [0]	6 (10.0) [1]
Deaths, SAEs, and Other SAEs		
Deaths, n (%)	0	0
Subjects with at least 1 SAE, n (%)	1 (1.8)	1 (1.7)
Subjects with at least 1 SAE by UCB SOC	**N (%) [n considered drug related by the investigator]**	
General disorders and administration site conditions	0	1 (1.7) [0]
Infections and infestations	1 (1.8) [0]	0
Subjects with AEs leading to permanent study drug discontinuation, n (%)	0	2 (3.3) [0]
Subjects with AEs leading to permanent study drug discontinuation by UCB SOC	**N (%) [n considered drug-related by the investigator]**	
Nervous system disorders	0	1 (1.7) [1]
Psychiatric disorders	0	1 (1.7) [1]

Primary & secondary outcomes:

Levetiracetam was statistically, significantly superior to PBO in reducing partial onset seizure frequency in subjects (1 month to less than 4 years of age) in the modified intent-to-treat (mITT) population. The LEV group response rate (responder rate in average daily frequency [ADF] for partial onset seizures) was 43.1% (25/58) as compared with 19.6% (10/51) for PBO.

Publication reference(s) based on the study:

Pina-Garza J, Nordli D, Jr., Rating D, et al. Efficacy and safety of levetiracetam oral solution as adjunctive treatment of refractory partial-onset seizures in pediatric epileptic patients aged 1 month to <4 years. Abstract No. 3.292. 62nd American Epilepsy Society Annual Meeting, 30 Nov - 4 Dec, 2007 (Philadelphia, PA).

Date of report: 27 Aug 2007