Approved by UCB 01-JUL-2008

Clinical Study Summary (CSS)

CT Registry ID#: NCT00105040
Study No.: N01103

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Based on Clinical Study Report document reference code: RRCE06E0906

Proprietary drug name	**INN:**	**Therapeutic area and indication(s)**
Keppra® Oral Tablets/Oral Solution	Levetiracetam	Partial onset seizures

Name of sponsor/company: UCB Inc.

Title of study:
A 19-week, randomized, double-blind, multicenter, placebo-controlled safety study to evaluate the cognitive and neuropsychological effects of levetiracetam 20 to 60mg/kg/d, divided in twice daily dosing, as adjunctive treatment in children 4 to 16 years old, inclusive, with partial onset seizures

Investigator(s) (number only): 45 initiated; 29 screened subjects; 28 enrolled subjects

Study center(s) (number only): 45 initiated; 29 screened subjects; 28 enrolled subjects

Length of study:	~19 weeks	**Phase of development:** Phase II
Date first patient enrolled:	27 Sep 2004	
Date last patient completed:	21 Mar 2007	

Abstract:

The objective of this study was to characterize potential cognitive and neuropsychological effects of levetiracetam (LEV) (20 to 60mg/kg/d) as adjunctive treatment in children 4 to 16 years old, inclusive, with partial onset seizures, as non-inferior when compared to adjunctive treatment with placebo (PBO).

Main criteria for inclusion:

- Pediatric subjects (4 to 16 years old) diagnosed with partial onset seizures for a minimum of 6 months prior to Visit 1 experiencing at least 1 partial onset seizure during the 4 weeks prior to Visit 1 were enrolled.
- Subjects were on a stable regimen of 1 or a maximum of 2 other antiepileptic drugs (AEDs) for at least 2 weeks prior to Visit 1.
- Subject must have an intelligence quotient (IQ) at baseline of at least 65.
- Subject and parent/guardian were fluent in English.

Main exclusion criteria:

- Subject must not have had previous treatment with LEV unless, in the opinion of the investigator, the subject's previous treatment was inadequate in dose or duration to provide an accurate assessment of the therapy, or the effect of LEV was confounded by concomitant medication.
- Subject receiving benzodiazepines on a routine or chronic basic and was unable to discontinue use 4 weeks prior to Visit 1.
- Subject received phenobarbital or primidone prior to Visit 1.
- Subject used felbamate for less than 18 months prior to Visit 1, if the subject was using felbamate.
- Subject had a current psychiatric disorder other than mild to moderate attention deficit, behavior, or learning disorders.

The randomization ratio was 2 (LEV) to 1 (PBO). Doses were titrated up to a maximum of 60mg/kg/d over 4 weeks. Subjects continued at their maximum dose for 8 weeks. Cognitive and neuropsychological testing, as well as other safety and efficacy assessments were performed at baseline and at the end of the Evaluation Period (Week 12). After the Evaluation Period subjects either entered a 6-week Withdrawal Period or they entered the open-label, long-term, follow-up study (N01148).

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Number of patients:	**PBO**	**LEV**
Planned, N:	29	58
Enrolled, N:	34	65
Number of patients (ITT), N:	34	64
Number of patients (PP), N:	27	46
Completed, n (%):	29 (85.3)	50 (78.1)
Withdrawn, n (%):	5 (14.7)	14 (21.9)
Withdrawn due to adverse events, n (%):	2 (5.9)	7 (10.9)
Withdrawn for other reasons, n (%):	3 (8.8)	7 (10.9)
Demography:		
Gender females /males, n (%):	17 (50)/17 (50)	25 (39.1)/39 (60.9)
Age (years), mean (SD):	10.27 (3.67)	10.58 (3.49)
Race, n (%):		
Caucasian	18 (52.9)	40 (62.5)
Black	8 (23.5)	15 (23.4)
Asian	3 (8.8)	3 (4.7)
Other/mixed race	5 (14.7)	6 (9.4)

Safety outcomes:
The proportion of subjects experiencing at least 1 adverse event (AE) was 89.1% in the LEV group compared with 85.3% in the PBO group. The proportion of subjects with treatment-related AEs was 51.6% in the LEV group compared with 41.2% in the PBO group. The treatment-emergent adverse events (TEAEs) that occurred in at least 10% of subjects in the LEV group and also occurred proportionally more often in the LEV group than the PBO group were headache (LEV 26.6%; PBO 14.7%), nasopharyngitis (LEV 15.6%; PBO 11.8%), fatigue (LEV 14.1%; PBO 11.8%), vomiting (LEV 14.1%; PBO 8.8%), somnolence (LEV 14.1%; PBO 8.8%), and aggression (LEV 12.5%; PBO 8.8%). No clinically relevant changes from baseline were observed in hematology, blood chemistry, vital signs, physical and neurological examinations, or electrocardiograms. Few subjects in either treatment group had possibly clinically significant (PCS) values for any of these safety variables. The pattern of TEAEs was consistent with current labeling for LEV. Overall, adjunctive treatment with LEV in this population (children 4 to 16 years of age with partial onset seizures) did not result in negative effects on cognitive functioning. Additionally, overall safety (including cognitive and neuropsychological effects), as measured by Leiter International Performance Scale-Revise (Leiter-R), Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2), Achenbach Child Behavior Checklist (CBCL), Child Health Questionnaire (CHQ-PF50), and standard safety measures were consistent with the current LEV label. Levetiracetam appeared to be safe and well tolerated when the standard clinical safety assessments were evaluated.

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Treatment-emergent AEs:	**PBO (N=34)**	**LEV (N=64)**
Total number of TEAEs	128	308
Subjects with at least 1 TEAE, n (%)	29 (85.3)	57 (89.1)
Subjects with at least 1 TEAE by UCB System organ class (SOC)[a]	**n (%) [n considered drug-related by the Investigator]**	
Blood and lymphatic system disorders	0	1 (1.6) [0]
Cardiac disorders	2 (5.9) [0]	2 (3.1) [1]
Ear and labyrinth disorders	2 (5.9) [0]	3 (4.7) [0]
Eye disorders	2 (5.9) [0]	2 (3.1) [0]
Gastrointestinal disorders	11 (32.4) [3]	23 (35.9) [8]
General disorders and administration site conditions	10 (29.4) [5]	14 (21.9) [6]
Immune system disorders	2 (5.9) [0]	3 (4.7) [0]
Infections and infestations	15 (44.1) [0]	30 (46.9) [0]
Injury, poisoning, and procedural complications	1 (2.9) [0]	8 (12.5) [1]
Metabolism and nutrition disorders	4 (11.8) [2]	7 (10.9) [3]
Musculoskeletal and connective tissue disorders	4 (11.8) [1]	5 (7.8) [1]
Nervous system disorders	16 (47.1) [11]	30 (46.9) [17]
Psychiatric disorders	7 (20.6) [7]	26 (40.6) [19]
Renal and urinary disorders	1 (2.9) [0]	4 (6.3) [3]
Reproductive system and breast disorders	1 (2.9) [0]	1 (1.6) [1]
Respiratory, thoracic, and mediastinal disorders	7 (20.6) [1]	14 (21.9) [0]
Skin and subcutaneous tissue disorders	10 (29.4) [2]	5 (7.8) [1]
Vascular disorders	2 (5.9) [1]	1 (1.6) [0]
Deaths	0	0
Subjects with at least 1 serious adverse event (SAE)	1 (2.9) [0]	0
Subjects with at least 1 SAE by UCB SOC		
Respiratory, thoracic, and mediastinal disorders	1 (2.9) [0]	0
Subjects with AEs that led to permanent study drug discontinuation by UCB SOC[a]		
Musculoskeletal and connective tissue disorders	0	1 (1.6) [1]
Nervous system disorders	1 (2.9) [1]	3 (4.7) [3]
Psychiatric disorders	1 (2.9) [1]	2 (3.1) [2]
Renal and urinary disorders	0	1 (1.6) [0]
Skin and subcutaneous tissue disorders	0	1 (1.6) [1]
Subjects with at least 1 psychiatric AE	7 (20.6) [7]	26 (40.6) [19]

[a] UCB SOC is different than the Primary System Organ Class assigned by MedDRA dictionary.

Primary & secondary outcomes:

In this study, the cognitive and neuropsychological effects of LEV 20 to 60mg/kg/d (as adjunctive treatment in children 4 to 16 years old, inclusive, with partial onset seizures) measured by the primary endpoint Leiter-R Memory Screen Composite Score were non-inferior when compared with adjunctive treatment with PBO. Additionally, 2-sided statistical tests for superiority using the secondary cognitive and neuropsychological WRAML-2 indexes concluded no statistically significant differences between the LEV and PBO groups. Exploratory efficacy evaluation demonstrated that adjunctive treatment with LEV resulted in better control of seizures than adjunctive treatment with PBO.

Publication reference(s) based on the study:

Mintz M, Hunter S, Yang H, et al. Double-blind, placebo-controlled, non-inferiority study to evaluate The cognitive and neuropsychological effects of levetiracetam 20-60 mg/kg/day as adjunctive treatment versus placebo in pediatric patients with partial-onset seizures. Abstract No. 3.293. 62nd American Epilepsy Society Annual Meeting, 30 Nov - 4 Dec, 2007 (Philadelphia, PA).

Date of report: 04 Jan 2008