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Clinical Study Summary

DEV/CCM/03126.2007

CT Registry ID#: NCT00160550
Study No.: N01057

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: RRCE05A3111

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

Name of Sponsor/Company: UCB Pharma SA

Title of Study:
A double-blind, multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of adjunctive treatment with 3000 mg/day (pediatric target dose of 60 mg/kg/day) oral levetiracetam (LEV) (166, 250 and 500 mg tablets), in adult and pediatric subjects (4 to 65 years) suffering from idiopathic generalized epilepsy with primary generalized tonic-clonic (PGTC) seizures

Investigator(s) (number only): 52

Study Center(s) (number only): 57

Length of Study:
Date first patient enrolled: 19-Sep-2001
Date last patient completed: 27-Jun-2005

Phase of Development: Phase III (therapeutic confirmatory)

Abstract:
The primary objective of this study was to assess the efficacy, safety, and tolerability of adjunctive treatment with levetiracetam (LEV) twice daily (b.i.d.) in subjects (aged 4 to 65 years) with PGTC seizures which were uncontrolled despite treatment with 1 or 2 concomitant anti-epileptic drugs (AEDs). Subjects were taking 1 or 2 concomitant AEDs, had idiopathic generalized epilepsy with uncontrolled PGTC seizures and ≥ 3 documented PGTC seizures during the 8-week combined baseline period. Subjects were given oral LEV 3000 mg/day (or a target dose of 60 mg/kg/day in children and adolescents <16 years and under 50 kg) or matching placebo (PBO). The treatment period consisted of a 4-week single-blind PBO baseline period; a 4-week up-titration period; a 20-week evaluation period; and a 6-week conversion/down-titration period (switching to an open-label follow-up study or down-titration, including a 2-week drug-free period). The primary efficacy variable was the percentage reduction from the combined baseline period (the 4-week historical baseline plus the 4-week prospective baseline) in the PGTC seizure frequency over the treatment period. The percentage reduction was 100*(B-T)÷B (B=the combined baseline period seizure frequency per week; T=the treatment period seizure frequency per week). Safety assessments included adverse events (AEs), laboratory tests (including AED levels), electrocardiogram (ECG), physical and neurological examinations, and vital signs. Body weight and height (for children < 16 years old) were included in vital sign measurements. Primary efficacy analysis was performed using an ANCOVA model with percent reduction as response, treatment as factor and baseline seizure frequency per week as covariate, with 2-tailed tests at the 0.05 significance level.

Number of Subjects:	**PBO**	**LEV**
Planned, N:	77	77
Enrolled, N:	84	80
Completed, n (%):	64 (76.2)	69 (86.3)
Number of Subjects Withdrawn, n (%):	20 (23.8)	11 (13.8)
Withdrawn due to Adverse Events, n (%):	7 (8.3)	2 (2.5)
Withdrawn for Other Reasons, n (%):	13 (15.5)	9 (11.3)

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Demography:	**PBO (N=84)**	**LEV (N=80)**
Gender (Females/Males):	45/39	46/34
Age (years), mean (SD):	30.59 (12.12)	26.89 (11.21)
Race, n (%):		
Caucasian	64 (76.2)	57 (71.3)
African/American	3 (3.6)	1 (1.3)
Hispanic	15 (17.9)	20 (25.0)
American Indian/Alaskan native	0	2 (2.5)
Other/mixed race	2 (2.4)	0

Safety Outcomes:

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

Overall, 57 subjects (72.2%) in the LEV group and 57 subjects (67.9%) in the PBO group experienced treatment emergent (TE)AEs. The most frequently reported TEAEs were infections and infestations (36.7% of LEV subjects and 31.0% of PBO subjects), psychiatric disorders (27.8% of LEV subjects and 25.0% of PBO subjects) and nervous system disorders (22.8% of LEV subjects and 23.8% of PBO subjects). Drug-related AEs were reported in 39.2% of the LEV-treated subjects and 29.8% of the PBO subjects. In total, 2 subjects (2.5%) in the LEV group and 7 subjects (8.3%) in the PBO group discontinued due to TEAEs. Psychiatric TEAEs that led to discontinuation were experienced by 2 subjects in the LEV group and 2 subjects in the PBO group.

No subjects died during the study. Post-treatment, 1 subject, with poorly controlled seizures, who had received LEV during the study, suffered a sudden death. It was considered unlikely to be a result of the study drug.

Overall, 3 subjects (3.8%) in the LEV group and 8 subjects (9.5%) in the PBO group experienced serious (S)AEs during the treatment period (uptitration and evaluation). Serious AEs suspected to be treatment-related were experienced by 2 subjects in the LEV group (aggression in 1 subject, and depression and a suicide attempt in the other subject), and 2 subjects in the PBO group (bradycardia and grand mal convulsion).

Eight subjects (10.1%) in the LEV group had abnormal hematology/blood chemistry or urine laboratory values that were judged clinically significant and were reported as TEAEs. For ECG abnormalities present at baseline, no clinically significant exacerbation was observed. In subjects with normal baseline measurements, no clinically significant ECG abnormalities were recorded during the study.

Treatment-Emergent AEs with during the treatment period:	**PBO N=84**	**LEV N=79**
Subjects with at least 1 TEAE, n (%):	57 (67.9)	57 (72.2)
UCB System Organ Class with an incidence of ≥ 10%	*n (%) [n considered drug-related by the Investigator]*	
Gastrointestinal disorders	18 (21.4) [4]	15 (19.0) [4]
General disorders and administration site conditions	8 (9.5) [5]	15 (19.0) [9]
Infections and infestations	26 (31.0) [4]	29 (36.7) [3]
Injury, poisoning and procedural complications	17 (20.2) [4]	11 (13.9) [2]
Metabolism and nutrition disorders	10 (11.9) [5]	7 (8.9) [3]
Musculoskeletal and connective tissue disorders	10 (11.9) [1]	7 (8.9) [0]
Nervous system disorders	20 (23.8) [8]	18 (22.8) [9]
Psychiatric disorders	21 (25.0) [12]	22 (27.8) [18]
Death, other SAEs:	**PBO (N=84)**	**LEV (N=79)**
Death, n (%):	0	0
Subjects with SAEs, n (%):	8 (9.5)	3 (3.8)
Subjects with SAEs (by UCB System Organ Class)	*n (%) [n considered drug-related by the Investigator]*	
Cardiac disorders	1 (1.2) [1]	1 (1.3) [0]
Gastrointestinal disorders	1 (1.2) [0]	0

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Infections and infestations	1 (1.2) [0]	1 (1.3) [0]
Injury, poisoning and procedural complications	2 (2.4) [0]	1 (1.3) [0]
Nervous system disorders	2 (2.4) [1]	0
Pregnancy, puerperium and perinatal conditions	1 (1.2) [0]	0
Psychiatric disorders	1 (1.2) [0]	1 (1.3) [1]
Primary Outcomes: There was a clinically significant difference between LEV and PBO treatment groups, in the percentage reduction in PGTC seizure frequency per week from the combined baseline to the treatment period (p=0.004).		
Percent reduction in PGTC seizure frequency per week, from combined baseline to treatment period	**PB0 (N=84)**	**LEV (N=78)**
Least square mean (SE)	28.19 (6.79)	56.49 (7.05)
Difference LEV-PBO [95% 2-sided CI]	28.31 [8.97, 47.64]	
p-value (ANCOVA)	0.004	
Publication Reference(s) based on the study: Berkovec et al. – Neurology 2007; waiting for publication		
Date of report: 27-Jul-2007		