Clinical Study Summary

DEV/CCM/03123.2007

CT Registry ID#: NCT00150735
Study No.: N01061

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Based on Clinical Study Report document reference code: RRCE04M1502

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

Name of Sponsor/Company: UCB Pharma SA

Title of Study:
A multicenter, double-blind, randomized, parallel-group, positive-controlled trial comparing the efficacy and safety of levetiracetam (1000 to 3000 mg/day oral b.i.d.) to carbamazepine (400 to 1200 mg/day oral b.i.d.), used as monotherapy for up to a maximum of 121 weeks in subjects (≥ 16 years) newly or recently diagnosed as suffering from epilepsy, and experiencing partial or generalized tonic-clonic seizures

Investigator(s) (number only): 85

Study Center(s) (number only): 85

Length of Study:
Date first patient enrolled: 20-Jun-2002
Date last patient completed: 12-Jul-2005

Phase of Development: Phase III (therapeutic confirmatory)

Abstract:
The primary objective of this study was to assess that monotherapy with levetiracetam 1000 to 3000 mg/day (LEV) was not inferior to monotherapy with carbamazepine 400 to 1200 mg/day (CBZ) in achieving 6-month seizure freedom (as the primary end point) in adults with newly or recently diagnosed epilepsy, and suffering from partial or generalized tonic-clonic seizures without clear focal origin. Subjects (≥ 16 years) were required to have had ≥ 2 seizures (partial seizures or generalized tonic-clonic seizures) in the year before randomization, with ≥ 1 seizure (partial seizure or generalized tonic-clonic seizure) in the 3 months preceding randomization, and not to have been treated for epilepsy in the past 6 months. Efficacy had to be assessed at the optimal dose: subjects had the opportunity to try 3 different dose levels based on the recurrence of seizures. Each dose was uptitrated over 2 weeks followed by 1 week of stabilization and a 6-month evaluation period at a stable dose. If 6-month seizure freedom was achieved, this period was followed by another period of 6 months for maintenance of seizure freedom. In case of a seizure during the evaluation period at the first 2 dose levels, the dose had be increased. The 3 dose levels were for LEV 1000 mg/day, 2000 mg/day and 3000 mg/day; for CBZ 400 mg/day, 800 mg/day and 1200 mg/day. The primary efficacy variable was the proportion of subjects from the per-protocol (PP) population with 6-month seizure freedom at the last evaluated dose. The LEV and CBZ groups were compared for the primary efficacy parameter by means of a logistic regression model, with treatment group and seizure category as factors. Parameters estimated from this model were used to derive an adjusted absolute difference (LEV–CBZ) and its 95% 2-sided confidence interval (CI). This CI was compared to the non-inferiority limit set to a priori –15%, to determine if LEV could be considered non-inferior to CBZ. Safety assessments consisted of adverse events (AEs), laboratory tests, electrocardiograms (ECGs), physical and neurological examinations, vital signs (including body weight), and psychiatric and mental status.

Number of Subjects:	**CBZ**	**LEV**
Planned, N:	290	290
Enrolled, N (ITT population):	291	288
Intent-To-Treat population, N	291	285
Completed, n (%):	156 (53.6)	154 (54.0)
Number of Subjects Withdrawn, n (%):	135 (46.4)	131 (46.0)
Withdrawn due to Adverse Events, n (%):	56 (19.2)	42 (14.7)
Withdrawn for Other Reasons*, n (%):	79 (27.1)	89 (31.2)

*lack of efficacy, lost to follow-up, protocol violation, withdrawal of consent, and other reasons

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Demography (ITT population):	**CBZ (N=291)**	**LEV (N=285)**
Gender (Females/Males):	120/171	139/146
Age (years), mean (SD):	39.04 (15.83)	39.79 (16.60)
Race, n (%)		
Caucasian	268 (92.1)	262 (91.9)
African/American	10 (3.4)	5 (1.8)
Asian/Pacific Islander	4 (1.4)	1 (0.4)
Other	9 (3.1)	17 (6.0)

Safety Outcomes:

Overall, during the randomized treatment period (dose-finding, evaluation and maintenance periods) treatment emergent (TE)AEs were experienced by 227 subjects (79.6%) in the LEV group and 235 subjects (80.8%) in the CBZ group. The most common TEAEs were nervous system disorders (40.4% of LEV subjects and 39.9% of CBZ subjects), infections and infestations (33.7% of LEV subjects and 32.0% of CBZ subjects), gastrointestinal disorders (25.6% of LEV subjects and 29.2% of CBZ subjects) and general disorders and administration site conditions (21.8% of LEV subjects and 21.3% of CBZ subjects).

Two deaths were reported during the study, both in the CBZ group: 1 subject died of a lung neoplasm and 1 subject died of a gunshot wound to the head. One LEV-treated subject died 2.5 months after stopping the study drug, having had 3 serious (S)AEs during the study: cerebrovascular accident; gait instability; and status epilepticus.

SAEs were experienced by 18 subjects (6.3%) in the LEV group and 29 subjects (10.0%) in the CBZ group. SAEs considered drug-related occurred in 1.1% of LEV subjects and 3.4% of CBZ subjects. Three pregnancies occurred during the study, all in the CBZ group. One pregnancy occurred in a subject taking oral contraceptives. Two ended by an induced abortion and 1 in a normal delivery. Adverse events leading to discontinuation of study drug occurred in 41 subjects (14.4%) in the LEV group and 56 subjects (19.2%) in the CBZ group. Most AEs leading to withdrawal were psychiatric disorders, nervous system disorders and skin and subcutaneous tissue disorders.

Abnormal laboratory values were distributed evenly between both treatment groups. No clinically meaningful changes from baseline were observed in vital signs. Similar numbers of occurrence of PCST (possibly clinically significant treatment-emergent) values for ECG QTc intervals were reported in both treatment groups. There was no evidence for concern about findings of significant repolarization abnormalities. Possibly clinically significant weight increases were observed in 21 subjects (7.8%) in the LEV group and 37 subjects (13.4%) in the CBZ group.

Treatment-Emergent AEs:	**CBZ (N=291)**	**LEV (N=285)**
Subjects with at least 1 TEAE, n (%):	235 (80.8)	227 (79.6)
UCB System Organ Class with an incidence of ≥ 10%	*n (%) [n considered drug-related by the Investigator]*	
Gastrointestinal disorders	85 (29.2) [59]	73 (25.6) [43]
General disorders and administration site conditions	62 (21.3) [46]	62 (21.8) [46]
Infections and infestations	93 (32.0) [5]	96 (33.7) [7]
Metabolism and nutrition disorders	33 (11.3) [23]	27 (9.5) [12]
Musculoskeletal and connective tissue disorders	45 (15.5) [9]	35 (12.3) [7]
Nervous system disorders	116 (39.9) [81]	115 (40.4) [74]
Psychiatric disorders	52 (17.9) [32]	72 (25.3) [45]
Skin and subcutaneous tissue disorders	49 (16.8) [39]	30 (10.5) [20]

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Death, other SAEs:	**CBZ (N=291)**	**LEV (N=285)**
Death, n (%):	2 (0.7%)	0
Subjects with SAEs, n (%):	29 (10.0)	18 (6.3)
Subjects with SAEs (SAE incidence ≥ 1%) (by UCB System Organ Class)	*n (%) [n considered drug-related by the Investigator]*	
Infections and infestations	3 (1.0) [0]	2 (0.7) [0]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.0) [0]	0
Nervous system disorders	6 (2.1) [1]	6 (2.1) [0]
Psychiatric disorders	4 (1.4) [1]	4 (1.4) [1]
Respiratory, thoracic and mediastinal disorders	3 (1.0) [0]	2 (0.7) [0]
Primary Outcome: At the last evaluated dose, 173 (73.0%) of the Per Protocol (PP) subjects in the LEV arm were seizure-free for at least 6 months, compared to 171 (72.8%) of the PP subjects in the CBZ arm. The adjusted absolute difference between LEV and CBZ (95% 2-sided CI) was 0.2% (–7.8%, 8.2%). The lower limit of the 95% 2-sided CI (-7.8%) was above the non-inferiority limit set as –15% in the protocol.		
6-month seizure freedom at the last evaluated dose	**CBZ (N=235)**	**LEV (N=237)**
n (%)	171 (72.8)	173 (73.0)
Adjusted difference (LEV – CBZ) [95% 2-sided CI]	0.2% [-7.8%, 8.2%]	
Publication Reference(s) based on the study: Brodie et al. – Neurology 2007; 68: 402-408		
Date of report: 27-Jul-2007		