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Clinical Study Summary (CSS)

CT Registry ID#: NCT00150748
Study No.: N167

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Based on Clinical Study Report document reference code: RRCE08H1201

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Keppra®	**Levetiracetam**	Primary generalized epilepsy

Name of Sponsor/Company: UCB Pharma SA

Title of Study: An open-label multicenter, follow-up study to evaluate the safety and efficacy of levetiracetam (LEV) (oral tablets of 166, 250, or 500mg bid) at individualized doses up to a maximum of 4000mg/day (or 80mg/kg/day for children and adolescents less than 50kg), in children (≥4 years old), adolescents, and adults suffering from primary generalized seizures

Investigators (number only): 69

Study Centers (number only): 69

Length of Study:	Mean: 781.0 days	Phase of Development: III
Date first patient enrolled:	01 Nov 2001	
Date last patient completed:	10 Jul 2007	

Abstract:
The objectives of the study were to evaluate the safety and efficacy of LEV at individualized doses with a maximum of 4000mg/day (or 80mg/kg/day for children and adolescents less than 50kg), in reducing seizures in children, adolescents, and adults suffering from primary generalized (type II) seizures.

Diagnosis and Main Criteria for Inclusions: Male/female children, adolescents, and adults completing one of the following were included in N167:

- The Final Visit of the double-blind N166 study
- The Final Visit of the double-blind N01057 study
- The Final Visit of the open-label follow-up N129 study
- The second-year Evaluation Visit of the open-label, follow-up N164 study

Number of Patients:	**Prior Study**	**Result**
Planned, N:	300	
Enrolled, N:	N01057/N166 N129/N164)	217 20
Completed, n (%):	N01057/N166 N129/N164	125 (57.6%) 3 (15.0%)
Number of Patients Withdrawn, n (%):	N01057/N166 N129/N164	92 (42.4%) 17 (85.0%)
Withdrawn due to Adverse Events, n (%):	N01057/N166 N129/N166	20 (9.2%) 0
Withdrawn for Lack of Efficacy, n (%):	N01057/N166 N129/N164	26 (12.0%) 0
Demography:		
Gender (Females/Males), n (%):	N01057/N166 N129/N164	126 (58.1%)/91 (41.9%) 11 (55.0%)/9 (45.0%)
Age Range (years), mean (SD):	N01057/N166 N129/N164	6.1-62.7, 27.99 (10.88) 6.2-49.3, 31.10 (12.28)

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Race, n (%):		
Caucasian	N01057/N166 N129/N164	161 (74.2%) 20 (100.0%)
Hispanic	N01057/N166 N129/N164	50 (23.0%) 0
Indian/Pakistani	N01057/N166 N129/N164	1 (0.5%) 0
American Indian/Alaskan Native	N01057/N166 N129/N164	2 (0.9%) 0
Other	N01057/N166 N129/N164	2 (0.9%) 0
Unknown	N01057/N166 N129/N164	1 (0.5%) 0
Weight range (kg), mean	N01057/N166 N129/N164	22.0-136.3, 70.68 22.0-150.5, 76.90
Height range (cm), mean	N01057/N166 N129/N164	114-194, 166.7 129-187, 166.8
Body Mass Index range (kg/m^2), mean	N01057/N166 N129/N164	14.5-47.2, 25.19 13.2-43.0, 26.89

Safety Outcomes:

For subjects from N01057/N166, 165 subjects (76.0%) in the Overall Pooled group experienced 848 TEAEs, and for subjects from N129/N164, 19 subjects (95.0%) in the Overall Pooled group experienced 126 TEAEs. Treatment-emergent AEs occurred most frequently in the Nervous system disorders (87 subjects [40.1%] from N01057/N166, and 10 subjects [50.0%] from N129/N164) and Infections and infestations (83 subjects [38.2%] from N01057/N166, and 14 subjects [70.0%] from N129/N164) UCB SOCs. The most frequently occurring TEAE preferred terms, in subjects from N01057/N166, were headache (40 subjects [18.4%]) and nasopharyngitis (24 subjects [11.1%]), and in subjects from N129/N164, was convulsion (6 subjects [30.0%]).

Most subjects experienced TEAEs that were mild or moderate in intensity. Of the 165 subjects (76.0%) in the Overall Pooled group from N01057 and N166 who experienced TEAEs, 29 subjects (13.4%) experienced severe TEAEs. Severe TEAEs occurred most frequently in the Nervous system disorders UCB SOC (13 subjects [6.0%]), and the TEAE preferred terms occurring most frequently were convulsion, headache, and status epilepticus (3 subjects each [1.4%]); and chest pain, grand mal convulsion, aggression, and depression (2 subjects each [0.9%]). Of 19 subjects (95.0%) from N129 and N164 who experienced TEAEs, 6 subjects (30.0%) experienced severe TEAEs. Severe TEAEs occurred most frequently in the Gastrointestinal disorders UCB SOC (3 subjects [15.0%]).

In subjects from N01057 and N166, 1 subject died (suicide) and 31 subjects (14.3%) experienced treatment-emergent SAEs; 10 subjects (4.6%) experienced treatment-emergent SAEs that were considered drug related by the Investigator. Treatment-emergent SAEs occurred most frequently in the Nervous system disorders UCB SOC (13 subjects [6.0%]), and the most frequently occurring SAE preferred terms were convulsion (7 subjects [3.2%]) and pregnancy (4 subjects [1.8%]). A total of 4 subjects (20.0%) from N129 and N164 experienced treatment-emergent SAEs. None of the treatment-emergent SAEs were drug related, and all SAE preferred terms (myoclonus, convulsion, abdominal pain, abortion spontaneous, and implant site infection) occurred in 1 subject each.

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Few subjects experienced TEAEs that led to permanent study drug discontinuation (17 subjects [7.8%] from N01057/N166 and no subjects from N129/N164), temporary study drug discontinuation (2 subjects [0.9%] from N01057/N166 and no subjects from N129/N164), or study drug dose change (10 subjects [4.6%] from N01057/N166, and 1 subject [5.0%] from N129/N164).

For subjects from N01057 and N166, treatment-emergent psychiatric AEs occurred most frequently in the following UCB high level grouping terms (HLGTs): Anxiety disorders (20 subjects [9.2%]) and Nonpsychotic mood disorders (19 subjects [8.8%]). The most frequently occurring treatment-emergent psychiatric AE preferred terms were: depression (16 subjects [7.4%]), insomnia (9 subjects [4.1%]), nervousness (8 subjects [3.7%]), and anxiety (7 subjects [3.2%]). All other treatment-emergent psychiatric AEs were reported in fewer than 3% of subjects (≤6 subjects). Five subjects from N129 experienced 7 treatment-emergent psychiatric AEs and no subject from N164 experienced treatment-emergent psychiatric AEs; stress symptoms and sleep disorder occurred in 2 subjects each, and suicidal ideation, anxiety, and depressed mood occurred in 1 subject each.

A total of 43 subjects from N01057 and N166 took at least 1 LEV dose ≥3500mg/24 hours during the study. The mean (median) duration of LEV dosing ≥3500mg/24 hours was 466.30 (415.95) days. The incidence of TEAEs was similar while subjects were taking LEV doses ≥3500mg/24 hours and <3500mg/24 hours, with a few exceptions. The incidence of TEAEs in the UCB SOC Infections and infestations was slightly higher while subjects were taking LEV doses ≥3500mg/24 hours (15 subjects [34.9%]), compared to the period when subjects were taking LEV doses <3500mg/24 hours (10 subjects [23.3%]). The incidence of the following TEAE preferred terms was slightly higher while subjects were taking LEV doses ≥3500mg/24 hours, compared to the period when subjects were taking LEV doses <3500mg/24 hours: headache (18.6% vs 7.0%); vomiting (7.0% vs 0%); fatigue (9.3% vs 2.3%); pyrexia (7.0% vs 2.3%); and neck pain, ataxia, and anxiety (4.7% vs 0% each). Only 1 TEAE (tremor) that occurred while the subject was taking a LEV dose ≥3500mg/24 hours resulted in permanent discontinuation from the study.

When the incidence of TEAEs by Baseline epileptic syndrome was examined, the Juvenile absence epilepsy plus childhood absence epilepsy subgroup had lower proportions of subjects with at least 1 TEAE (48.4%), with severe TEAEs (6.5%), and with serious TEAEs (6.5%), compared to the other Baseline epileptic syndrome subgroups. The Other idiopathic generalized epilepsies subgroup had higher proportions of subjects with TEAEs that led to dose change (13.6%) and with drug-related TEAEs (50.0%), compared to the other Baseline epileptic syndrome subgroups.

Few TEAEs related to laboratory values (hematology and blood chemistry) were reported (none were serious), and few possibly clinically significant (PCS) laboratory values were observed during the study.

Few TEAEs related to blood pressure and heart rate were reported during the study (1 event of pyrexia was serious), and few PCS blood pressure and heart rate values were observed during the study. More than half the subjects (125 subjects [57.6%] from N01057/N166 and 12 subjects [70.6%] from N129/N164) reported treatment-emergent PCS weight values during the study: 83 subjects (38.2%) with PCS weight values too high and 48 subjects (22.1%) with PCS weight values too low from N01057/N166; and 10 subjects (58.8%) with PCS weight values too high and 2 subjects (11.8%) with PCS weight values too low from N129/N164. The most frequently reported vital sign-related TEAE was weight increased (17 subjects [7.8%] from N01057/N166 and 2 subjects [10.0%] from N129/N164).

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For all ECG parameters, slight changes from Baseline in mean and median values during the study returned towards Baseline values while still receiving LEV treatment (at the last value on treatment). Few TEAEs related to ECGs were reported during the study (1 subject experienced SAEs of arrhythmia and atrial fibrillation). The most frequently reported shift from not PCS at Baseline to treatment-emergent PCS for subjects from N01057 and N166 was QRS interval too high (62 subjects [29.0%]). Most subjects with PCS QRS interval too high had values ≤100msec, and no TEAEs related to QRS were reported. In subjects from N129 and N164, treatment-emergent PCS QRS interval value too high (regardless of Baseline value) was also most frequently reported (6 subjects [35.3%]).

Treatment-Emergent AEs (TEAEs):	**Prior Study**	**Result**
Patients with at least one TEAE, n (%):	N01057/N166 N129/N164	165 (76.0%) 19 (95.0%)

TEAEs reported in >5% of patients	
UCB System Organ Class **Preferred Term**	**Overall Pooled (LEV-treated)** ***n (%) [n considered drug related by the Investigator]***
From N01057/N166	**N=217**
Gastrointestinal disorders	
Vomiting	13 (6.0%) [1]
Infections and infestations	
Nasopharyngitis	24 (11.1%) [3]
Influenza	20 (9.2%) [2]
Urinary tract infection	13 (6.0%) [1]
Metabolism and nutrition disorders	
Weight increased[(a)]	17 (7.8%) [8]
Nervous system disorders	
Headache	40 (18.4%) [10]
Dizziness	18 (8.3%) [9]
Tremor	15 (6.9%) [4]
Convulsion	13 (6.0%) [2]
Psychiatric disorders	
Depression	16 (7.4%) [9]
From N129/N164	**N=20**
Gastrointestinal disorders	
Diarrhoea	3 (15.0%) [0]
Abdominal pain	2 (10.0%) [0]
Constipation	2 (10.0%) [0]
Infections and infestations	
Ear infection	3 (15.0%) [0]
Respiratory tract infection	3 (15.0%) [0]
Bronchitis	2 (10.0%) [0]
Gastroenteritis	2 (10.0%) [0]
Influenza	2 (10.0%) [0]
Nasopharyngitis	2 (10.0%) [0]
Urinary tract infection	2 (10.0%) [0]
Viral upper respiratory tract infection	2 (10.0%) [0]
Injury, poisoning, and procedural complications	
Contusion	2 (10.0%) [0]
Metabolism and nutrition disorders	
Weight increased[(a)]	2 (10.0%) [0]

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CT Registry ID#: NCT00150748 **Study No.:** N167		
Nervous system disorders		
Convulsion	6 (30.0%) [0]	
Dizziness	2 (10.0%) [2]	
Headache	2 (10.0%) [0]	
Psychiatric disorders		
Sleep disorder	2 (10.0%) [0]	
Stress symptoms	2 (10.0%) [0]	
Reproductive system and breast disorders		
Dysmenorrhoea	2 (10.0%) [0]	
Respiratory, thoracic, and mediastinal disorders		
Sinus pain	2 (10.0%) [0]	
[(a)] The system organ class for this preferred term is different from the Medical Dictionary for Regulatory Activities (MedDRA®) primary system organ class		
Death, SAEs, and Other SAEs:	**Prior Study**	**Result**
Death, n (%):	N01057/N166 N129/N164	1 (0.5%) 0
Patients with treatment-emergent SAEs, n (%):	N01057/N166 N129/N164	31 (14.3%) 4 (20.0%)
Patients with SAEs ***UCB System Organ Class*** ***Preferred Term***	***n (%) [n considered drug related by the Investigator]***	
From N01057/N166	**N=217**	
Cardiac disorders		
Arrhythmia	1 (0.5%) [1]	
Atrial fibrillation	1 (0.5%) [1]	
General disorders and administration site conditions		
Multi-organ failure	1 (0.5%) [0]	
Pyrexia	1 (0.5%) [0]	
Ulcer	1 (0.5%) [0]	
Infections and infestations		
Appendicitis	1 (0.5%) [0]	
Injury, poisoning, and procedural complications		
Concussion	1 (0.5%) [0]	
Eye injury	1 (0.5%) [0]	
Hand fracture	1 (0.5%) [1]	
Joint dislocation	1 (0.5%) [0]	
Scapula fracture	1 (0.5%) [0]	
Wrist fracture	1 (0.5%) [1]	
Musculoskeletal and connective tissue disorders		
Osteoarthritis	1 (0.5%) [0]	
Scoliosis	1 (0.5%) [0]	

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Nervous system disorders	
Coma	1 (0.5%) [0]
Convulsion	7 (3.2%) [1]
Epilepsy	1 (0.5%) [1]
Grand mal convulsion	2 (0.9%) [0]
Headache	1 (0.5%) [1]
Postictal state	1 (0.5%) [0]
Status epilepticus	2 (0.9%) [1]
Pregnancy, puerperium, and perinatal conditions	
Abortion	1 (0.5%) [0]
Abortion induced[(a)]	1 (0.5%) [0]
Intra-uterine death	1 (0.5%) [1]
Pregnancy	4 (1.8%) [0]
Premature baby	1 (0.5%) [0]
Unintended pregnancy	2 (0.9%) [0]
Psychiatric disorders	
Completed suicide	1 (0.5%) [0]
Depression	1 (0.5%) [1]
Psychotic disorder	1 (0.5%) [1]
Schizophrenia	1 (0.5%) [1]
Suicidal ideation	1 (0.5%) [1]
Skin and subcutaneous tissue disorders	
Rash erythematous	1 (0.5%) [1]
Vascular disorders	
Deep vein thrombosis	1 (0.5%) [0]
From N129/N164	**N=20**
Gastrointestinal disorders	
Abdominal pain	1 (5.0%) [0]
Infections and infestations	
Implant site infection	1 (5.0%) [0]
Nervous system disorders	
Myoclonus	1 (5.0%) [0]
Convulsion	1 (5.0%) [0]
Pregnancy, puerperium, and perinatal conditions	
Abortion spontaneous	1 (5.0%) [0]

Primary & Secondary Outcomes:

The majority of subjects (56.2% and 60.0% of subjects from N01057/N166 and N129/N164, respectively) in the Overall Pooled group had at least 1 maximum all seizure freedom interval of at least 6 months, the primary efficacy variable.

For the secondary efficacy variables:

- In the Intent-to-Treat (ITT) population (N01057/N166), 31.3% of subjects had an all seizure freedom interval of at least 6 months from the beginning of the study (N167 Visit 1), and 22.6% had complete seizure freedom during the Evaluation Period. Results were similar for the absence (IIA), myoclonic (IIB), and tonic-clonic (IIE) seizure types in the Absence, Myoclonic, and Tonic-Clonic subpopulations.

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- For seizure days/frequency per week, mixed model repeated measures least squares analyses showed fewer seizures were reported during N167, compared to prior study Baseline, in the ITT population (N01057/N166), and the Absence, Myoclonic, and Tonic-Clonic subpopulations, and the seizure days/frequency appeared stable over the entire Evaluation Period.
- Responders were defined as subjects with a 50% to 100% reduction from Baseline in seizure days/frequency per week during the Evaluation Period. The majority of subjects were responders in the Overall Pooled group in the ITT population (N01057/N166) (79.7%), and Absence (75.7%), Myoclonic (84.3%), and Tonic-Clonic (82.9%) subpopulations. The majority of subjects in the ITT population (N01057/N166), and the Absence, Myoclonic, and Tonic-Clonic subpopulations who were responders had >75% reduction from Baseline in seizure days/frequency per week.

The exploratory variables, the Patient Quality of Life Inventory in Epilepsy - 31 (QOLIE-31-P) scores, showed improvement or stability in patient functioning and health-related quality of life over the entire treatment period.

Publication Reference(s) based on the study: None

Date of report: 02-Dec-2008