Clinical Study Summary (CSS)

CT Registry ID#: NCT00150709
Study No.: N157

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Based on Clinical Study Report document reference code: RRCE06E0908

Proprietary drug name	**INN**	**Therapeutic area and indication(s)**
Keppra® Oral Tablets/Oral Solution	Levetiracetam	Adjunctive treatment of epilepsy in pediatric subjects

Name of sponsor/company: UCB Inc.

Title of study: A multi-center, open-label, long-term, follow-up study of the safety and efficacy of levetiracetam (ucb L059) in children with epilepsy

Investigator(s) (number only): 55 were initiated and 50 enrolled at least one subject

Study center(s) (number only): 55 centers were initiated and 50 enrolled at least one subject

Length of study:	Varied from time of enrollment until pediatric market approval	**Phase of development:** Phase III
Date first subject enrolled:	26 Jan 1998	
Date last subject completed:	25 Jan 2006	

Abstract:
The objectives of this study were to allow pediatric subjects who participated in a previous trial of levetiracetam (LEV) the opportunity to receive open-label LEV treatment, to ensure the safety of study participants by provision for standardized follow-up, and to obtain standardized descriptive safety and efficacy data in pediatric subjects with epilepsy during long-term treatment with LEV at individualized doses.

Main inclusion criteria:

- Have completed a previous applicable LEV pediatric study.
- Treatment with LEV was considered to be of potential benefit such that the subject/parent(s)/legal guardian and the investigator agreed to continue treatment.

Main exclusion criteria:

- Was on a ketogenic diet (during the course of this study).
- Seizures were too close together to accurately count.

The study consisted of a Screening Phase (Visit 1) to determine subject eligibility, up to a 6-week Titration Phase for subjects entering from the double-blind study, and a Maintenance Phase during which subjects could take open-label LEV until market approval or until development of LEV in the pediatric indication was completed. When the subject or investigator decided to stop treatment with LEV, the subject was to enter the Withdrawal Phase, during which the dose of LEV was to be gradually reduced by 10 to 20 mg/kg/day every 2 weeks. A Final Visit was to be completed 2 weeks after the last intake of LEV.

Number of patients:	
Planned, N:	N/A[a]
Enrolled, N:	223[b]
Ongoing at study close-out, n (%):	74 (33.2)
Withdrawn, n (%):	149 (66.8)
Withdrawn due to adverse events, n (%):	15 (6.7)
Withdrawn for lack of efficacy, n (%):	26 (11.7)

Number of patients:	
Withdrawn for loss of efficacy, n (%):	26 (11.7)
Withdrawal of subject's consent	22 (9.9)
Lost to follow-up	5 (2.2)
Decision of UCB	1 (0.4)
Other[c]	35 (15.7)
Protocol violation	19 (8.5)
Demography:	
Gender (females/males) n (%):	105 (47.1)/118 (52.9)
Age range (years), [mean]:	0.2 to 17.5; [9.68]
Race, n (%):	
Caucasian	151 (67.7)
Hispanic	30 (13.5)
Black	27 (12.1)
Asian/Oriental	3 (1.3)
Other	12 (5.4)
Weight range (kg), (mean):	5.9 to 86.5 (35.7)
Height range (cm), (mean):	58.8 to 189 (133.7)
Body Mass Index (BMI) range (kg/m^2) (mean)	9.0 to 36.1 (18.8)

[a] The sample size for this study was not prospectively defined as enrollment was dependent upon the number of subjects who completed previous studies and chose to enroll.
[b] A total of 238 subjects were exposed. All 15 subjects from one site were excluded due to unreliability of the data reported.
[C] "Other" included study closure, parent's decision, investigator's decision, subject moved out of town, subject enrolling in another study, difficulty swallowing study medication, subject undergoing surgery for seizures, and incomplete efficacy.

Safety outcomes:

Overall, 218 subjects (97.8%) experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs (those that occurred in at least 20% of subjects) were infection 124 subjects (55.6%), fever 65 subjects (29.1%), headache 57 subjects (25.6%), accidental injury 56 subjects (25.1%), pharyngitis 55 subjects (24.7%), somnolence 52 subjects (23.3%), otitis media 52 subjects (23.3%), and vomiting 47 subjects (21.1%). The most common psychiatric AEs (those that occurred in more than 10% of subjects) were insomnia (13.9%), personality disorder (13.5%), hostility (11.2%), and nervousness (10.3%). Most TEAEs were reported as mild or moderate in intensity. Overall, 66 subjects (29.6%) reported at least 1 TEAE classified as severe. The most common treatment-related TEAEs were somnolence (13.0%), personality disorder (7.6%), and hostility (7.2%). These observations are consistent with the known safety profile of LEV.

No treatment-related deaths were reported. One subject died during the study due to AEs that the Investigator indicated were not related to LEV (status epilepticus, heart arrest, cardiopulmonary arrest, and multisystem organ failure). Treatment-emergent serious adverse events (SAEs) occurred in 74 subjects (33.2%). Treatment-emergent, treatment-related SAEs occurred in 9 subjects (4.0%). The most common SAEs were convulsions (9.9%), therapeutic epilepsy procedures (6.7%), and diagnostic epilepsy procedures (5.4%). The remaining SAEs occurred in less than 2% of subjects.

A total of 61 subjects (27.4%) had TEAEs leading to dose reduction, and 10 (4.5%) of these subjects permanently discontinued study drug. Somnolence led to permanent study drug discontinuation or dose reduction in 14 subjects (6.3%), and headache and diagnostic epilepsy procedures led to permanent study drug discontinuation or dose reduction in 5 subjects (2.2%) each.

For laboratory parameters, vital signs, and electrocardiograms, most findings were incidental, consistent with findings in adult LEV studies, and not unexpected considering the length of the study. There were no noteworthy findings from physical or neurological examinations.

Levetiracetam was well tolerated and safe when administered as a wide range of total daily doses over long-term.

TEAEs reported in >5% of LEV-treated Subjects:	
COSTART body system[a] preferred term	**LEV (n = 223) n (%) [n considered drug related by the Investigator]**
Body as a whole	
Abdominal pain	28 (12.6) [4]
Accidental injury	56 (25.1) [0]
Allergic reaction	21 (9.4) [0]
Asthenia	22 (9.9) [14]
Fever	65 (29.1) [2]
Flu syndrome	22 (9.9) [0]
Headache	57 (25.6) [13]
Hostility	25 (11.2) [16]
Infection	124 (55.6) [5]
Pain	30 (13.5) [0]
Viral infection	20 (9.0) [1]
Digestive system	
Anorexia	25 (11.2) [8]
Constipation	21 (9.4) [2]
Diarrhea	28 (12.6) [1]
Gastroenteritis	32 (14.3) [1]
Nausea	14 (6.3) [3]
Vomiting	47 (21.1) [4]
Hemic and lymphatic system	
Ecchymosis	14 (6.3) [1]
Metabolic and nutritional disorders	
Weight gain	14 (6.3) [4]
Weight loss	16 (7.2) [3]
Musculoskeletal system	
Pathological fracture	13 (5.8) [0]
Nervous system	
Agitation	12 (5.4) [5]
Convulsion	42 (18.8) [8]
Depression	13 (5.8) [8]
Dizziness	18 (8.1) [9]
Emotional lability	17 (7.6) [12]
Hyperkinesia	13 (5.8) [3]
Insomnia	31 (13.9) [9]
Nervousness	23 (10.3) [14]
Personality disorder	30 (13.5) [17]
Somnolence	52 (23.3) [29]
Thinking abnormal	18 (8.1) [11]
Procedure	
Procedure diagnostic epilepsy	12 (5.4) [0]
Procedure therapeutic epilepsy	16 (7.2) [0]
Respiratory system	
Cough increased	30 (13.5) [3]
Epistaxis	15 (6.7) [0]
Pharyngitis	55 (24.7) [2]
Pneumonia	13 (5.8) [0]
Rhinitis	42 (18.8) [2]
Sinusitis	30 (13.5) [1]
Skin and appendages	
Rash	27 (12.1) [1]
Special senses	
Otitis media	52 (23.3) [1]
Urogenital system	
Urine abnormality	12 (5.4) [3]

[a]Coding Symbols for a Thesaurus of Adverse Reaction Terms

Death, SAEs, and Other SAEs:	
Death, n (%):	1 (0.4)
Patients with SAEs, n (%):	74 (33.2)
Patients with SAEs considered drug-related by the investigator, n (%):	9 (4.0)
Patients with SAEs (by body system and COSTART preferred term):	**n (%) [n considered drug related by the investigator]**
Body as a whole	
Asthenia	1 (0.4) [1]
Cyst	1 (0.4) [0]
Hypothermia	1 (0.4) [0]
Fever	2 (0.9) [0]
Infection	1 (0.4) [0]
Infection bacterial	1 (0.4) [0]
Overdose	2 (0.9) [1]
Reaction unevaluable	1 (0.4) [0]
Cardiovascular system	
Heart arrest	1 (0.4) [0]
Hemorrhage	1 (0.4) [0]
Digestive system	
Constipation	1 (0.4) [0]
Fecal impaction	2 (0.9) [0]
Gastroenteritis	3 (1.3) [0]
Gastrointestinal disorder	1 (0.4) [0]
Hematemesis	1 (0.4) [0]
Ileitis	1 (0.4) [0]
Increased salivation	1 (0.4) [0]
Stomach atony	1 (0.4) [0]
Vomiting	1 (0.4) [0]
Endocrine system	
Diabetes mellitus	1 (0.4) [0]
Hemic and lymphatic system	
Lymphocytosis	1 (0.4) [0]
Metabolic and nutritional disorders	
Albuminuria	1 (0.4) [0]
Dehydration	2 (0.9) [0]
Weight loss	1 (0.4) [0]
Musculoskeletal system	
Musculoskeletal congenital anomaly	2 (0.9) [0]
Myasthenia	1 (0.4) [0]
Pathological fracture	2 (0.9) [0]
Nervous system	
Anxiety	1 (0.4) [1]
Antisocial reaction	1 (0.4) [1]
Apathy	1 (0.4) [1]
Convulsion	22 (9.9) [2]
Depression	3 (1.3) [3]
Intracranial hypertension	1 (0.4) [0]
Nervousness	1 (0.4) [1]
Personality disorder	3 (1.3) [1]
Psychosis	2 (0.9) [0]
Psychotic depression	1 (0.4) [1]
Schizophrenic reaction	1 (0.4) [0]
Somnolence	1 (0.4) [1]
Status epilepticus not otherwise specified (NOS)	3 (1.3) [0]
Status epilepticus partial	2 (0.9) [0]

Death, SAEs, and Other SAEs:	
Procedure	
Procedure diagnostic epilepsy	12 (5.4) [0]
Procedure diagnostic NOS	4 (1.8) [0]
Procedure therapeutic epilepsy	15 (6.7) [0]
Procedure therapeutic NOS	3 (1.3) [0]
Respiratory system	
Dyspnea	1 (0.4) [0]
Pneumonia	1 (0.4) [0]
Respiratory disorder	1 (0.4) [0]
Sinusitis	1 (0.4) [0]
Skin and appendages	
Herpes zoster	1 (0.4) [0]
Rash	1 (0.4) [1]
Urogenital system	
Kidney calculus	2 (0.9) [0]
Pyelonephritis	1 (0.4) [0]
Urogenital disorder	1 (0.4) [0]

Primary & secondary outcomes:

The primary analysis and the responder analyses were conducted on 203 subjects with baseline seizure counts. A median percentage reduction from baseline in partial onset seizure frequency per week was consistently maintained above 50% over the entire Treatment Period (mean and median exposure in N157 were approximately 2 years; maximum exposure was approximately 7.5 years).

Publication reference(s) based on the study: None

Date of report: 25 Oct 2007