Clinical Study Summary

DEV/CCM/03453.2007

CT Registry ID#: NCT00544050
Study No.: N01052

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Based on Clinical Study Report document reference code: RRCE03H2101

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

Name of Sponsor/Company: UCB Pharma SA

Title of Study: An open-label, single dose, pharmacokinetic study of 20 mg/kg of levetiracetam oral solution in epileptic pediatric subjects ranging in age from 1 month to less than 4 years old

Investigator(s) (number only): 7

Study Center(s) (number only): 7

Length of Study:
Date first patient enrolled: 18-Sep-2002
Date last patient completed: 15-May-2003

Phase of Development: Phase II (therapeutic exploratory)

Abstract:
The primary objective of this study was to document the pharmacokinetic (PK) parameters of both levetiracetam (LEV) and its metabolite (ucb L057) in epileptic pediatric subjects (aged 1 month up to 4 years) after a single dose of LEV 20 mg/kg. To be eligible for inclusion in the study, subjects had a diagnosis of epilepsy, weighed ≥ 5 kg, and were using no more than 2 antiepileptic drugs (AEDs). Subjects with a treatable seizure etiology, epilepsy secondary to progressive cerebral disease or other progressively neurodegenerative disease, a history of status epilepticus requiring hospitalization within 2 weeks prior to screening, or a disorder that would interfere with absorption, distribution, metabolism, or excretion of drugs were excluded. Plasma levels of LEV were used to determine the maximum measured plasma concentration (C_{max}), time at which C_{max} occurred (t_{max}), area under the curve from zero to infinity (AUC), area under the curve from time 0 to last quantifiable time point [$AUC_{(0-t)}$], terminal elimination rate consent (λ_z), elimination half-life associated with λ_z ($t_{½}$), apparent plasma clearance (CL/f), CL/f normalized for body weight and body surface area, apparent volume of distribution (Vd/f), and Vd/f normalized for body weight. Plasma levels of ucb L057 were used to determine C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, λ_z, and $t_{½}$. Safety assessments included adverse event (AE) monitoring, clinical laboratory assessments, clinical assessments (physical examinations, vital signs, body weight, height/length, head circumference), neurological examinations, and electrocardiograms (ECGs). Descriptive statistics were used to summarize plasma concentrations of LEV and ucb L057 at individual sampling times. The PK parameters were determined for both LEV and ucb L057 using the conventional non-compartmental method.

Number of Subjects:	**LEV 20 mg/kg**
Planned, N:	12
Enrolled, N (Intent-to-Treat population):	13
Completed, n (%):	13 (100)
Number of Subjects Withdrawn, n (%):	0

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Demography:	**LEV 20 mg/kg (N= 13)**
Gender (Females/Males):	6/7
Age (months), mean (SD):	19.9 (14.2)
Race, n (%)	
Caucasian	6 (46.2)
African-American	3 (23.1)
Hispanic	4 (30.8)

Safety Outcomes:

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

There were no deaths, serious AEs, or AEs leading to withdrawal from the study. During treatment with LEV 20 mg/kg, 3 subjects (23%) reported a total of 4 treatment emergent (TE)AEs. All 4 TEAEs were of mild or moderate intensity, and were considered, by the investigators, not related to study medication. Abnormal laboratory values were considered, by the investigators, not to be clinically significant. No clinically relevant changes were observed in vital signs, ECGs, neurological examinations, or physical examinations. LEV was well tolerated during this study, and safety assessments were consistent with the established safety profile of LEV.

Treatment-Emergent AEs:	**LEV 20 mg/kg (N=13)**
Subjects with at least 1 TEAE, n (%):	3 (23.1)
MedDRA Primary System Organ Class	*n (%) [n considered drug-related by the Investigator]*
Gastrointestinal disorders	1 (7.7) [0]
General Disorders and Administration Site Conditions	1 (7.7) [0]
Skin and Subcutaneous Tissue Disorders	1 (7.7) [0]

Primary Outcomes:

For levetiracetam, the mean C_{max} was 31.3 µg/mL, the median t_{max} was 1.0 h, and mean $t_{1/2}$ was 5.3 h. The mean C_{max} and $t_{1/2}$ for ucb L057 were 0.5 µg eq LEV/mL and 6.9 h, respectively, and the median t_{max} was 4.0 h. The PK results indicated that $t_{1/2}$ was shorter for these pediatric subjects (5.3 hours) than it was for adults (7.2 hours), and apparent clearance was faster (1.5 mL/min/kg pediatrics; 0.96 mL/min/kg adults). The results for the entire study population were consistent with observations in pediatric subjects aged 5 to 12 years. The exposure to ucb L057, as assessed by C_{max} and AUC equated for a 1 mg/kg dose, was lower in children than in adults.

Publication Reference(s) based on the study: Glauser et al. – Epilepsia 2007; 48(6): 1117-1122

Date of report: 26-Jul-2007