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Clinical Study Summary (CSS)

DEV/SGE/03944.2007

CT Registry ID#: NCT00600509
Study No.: N165

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: RRCE04C3001

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

Name of Sponsor/Company: UCB Japan Co., Ltd

Title of Study:
Bridging study of L059 (Levetiracetam) in patients with epilepsy by double blind method

Investigator(s) (number only): Not specified in the CSR

Study Center(s) (number only): 73

Length of Study:
Date first patient enrolled: 17-Jan-2001
Date last patient completed: 31-Jul-2003

Phase of Development: Phase II (Therapeutic confirmation)

Abstract:
The objective of this study was to evaluate the efficacy and the safety of levetiracetam (LEV) as add-on treatment in treatment-refractory epileptic Japanese subjects with partial onset seizures. The primary efficacy variable was the partial (type I) seizure frequency per week over the evaluation period. Safety assessments included monitoring of adverse events (AEs), safety laboratory tests, physical examinations (including vital signs), electrocardiograms (ECGs), plasma levels of LEV and of concomitant antiepileptic drugs (AEDs). Subjects were to be epileptic subjects (16 to 65 years old) experiencing simple and/or complex partial seizures with or without secondary generalization, had a minimum of 12 partial seizures during the 12-week baseline period, with a minimum of 2 partial seizures per 4 weeks, and had an existing treatment with 1 to 3 concomitant standard AEDs. Subjects were randomized to receive 1000 mg LEV, 3000 mg LEV or placebo (PBO). The study consisted of a 12-week baseline period, a 4-week up-titration, a 12-week evaluation and a 4-week down-titration or a 6-week transition period to open label LEV in a long term follow-up study. Analyses were performed on the FAS population, which included all randomized subjects who took at least one dose of study medication and excluded misallocations to study treatment. The primary efficacy analysis was the comparison of POS seizure frequency per week over the evaluation period between treatment groups through an ANCOVA model. The model was applied on $\log_e (x + 1)$ transformed seizure frequency, including treatment as a factor and $\log_e (x + 1)$ transformed baseline seizure frequency per week as a covariate. The difference in treatment LSmeans with a 2-sided 95% CI was computed and expressed as a percent reduction over placebo (= 100 x (1 - exp (LSmean Lev – LSmean PBO))).

Number of Subjects:	**PBO**	**LEV 1000 mg**	**LEV 3000 mg**
Planned, N:	70	70	70
Randomized, N:	72	73	71
Full Analysis Set (FAS), N:	70[(a)]	72[(b)]	71
Completed, n (%):	57 (81.4)	56 (77.8)	57 (80.3)
Number of Subjects Withdrawn, n (%):	13 (18.6)	16 (22.2)	14 (19.7)
Withdrawn due to Adverse Events, n (%):	7 (10.0)	9 (12.5)	5 (7.0)
Withdrawn for Other Reasons, n (%):	6 (8.6)	7 (9.7)	9 (12.7)

[(a)] Two subjects were excluded from the FAS population due to misallocation.

[(b)] One subject discontinued the trial prior to first study medication intake.

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Demography:	**PBO (N=70)**	**LEV 1000 mg (N=72)**	**LEV 3000 mg (N=71)**
Gender (Females/Males):	36/34	33/39	35/36
Age (years), mean (SD):	34.00 (10.31)	33.88 (10.72)	31.94 (10.28)
Race, n (%):			
Asian/Pacific Islander:	70 (100)	72 (100)	71 (100)

Safety Outcomes:

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

Overall, treatment-emergent (TE) AEs were reported for 83.3% and 84.5% of the subjects in 1000 mg and 3000 mg LEV groups, respectively versus 81.4% of the subjects in the PBO group. The most common reported TEAEs in LEV 1000 mg, LEV 3000 mg and PBO groups were infections and infestations (31.9%, 28.2%, and 28.6%, respectively), nervous system disorders (36.1% 21.1% and 20.0%, respectively), investigations (22.2%, 16.9% and 21.4%, respectively), and injury, poisoning and procedural complications (22.2%; 16.9%, and 11.4%, respectively). TEAEs considered to related to the study drug per definition in Japan (i.e., relationship to the study drug other than none) by the Investigator were reported for 56.9%, 54.9%, and 50.0% of the subjects in the LEV 1000 mg, 3000 mg and PBO groups, respectively.

There were no deaths during the trial. Serious AEs (SAEs) were reported by 5 subjects in the LEV 1000 mg group, 1 subject in the LEV 3000 mg group and 1 subject in the PBO group. All five (6.9%) subjects in the LEV 1000 mg group reported an SAE considered to be at least unlikely related to the study drug. TEAEs leading to permanent drug discontinuation were reported for 12.5% of the subjects in the LEV 1000 mg group, 8.5% of the subjects in the LEV 3000 mg group and 8.6% of the PBO-treated subjects.

Treatment Emergent AEs (TEAE) during up-titration and evaluation periods:	**PBO (N=70)**	**LEV 1000 mg (N=72)**	**LEV 3000 mg (N=71)**
Subjects with at least one TEAE, n (%):	57 (81.4)	60 (83.3)	60 (84.5)
Primary system Organ Class with an incidence of ≥ 15%	*n (%) [n considered drug-related by the Investigator]*		
Infections and infestations	20 (28.6) [10]	23 (31.9) [9]	20 (28.2) [6]
Nervous system disorders	14 (20.0) [9]	26 (36.1) [21]	15 (21.1) [12]
Investigations	15 (21.4) [10]	16 (22.2) [9]	12 (16.9) [11]
Injury, poisoning and procedural complications	8 (11.4) [1]	16 (22.2) [7]	12 (16.9) [0]
Skin and subcutaneous tissue disorders	6 (8.6) [0]	12 (16.7) [6]	14 (19.7) [5]
Gastrointestinal disorders	12 (17.1) [7]	10 (13.9) [8]	9 (12.7) [7]
Respiratory, thoracic and mediastinal disorders	8 (11.4) [3]	12 (16.7) [1]	11 (15.5) [4]
Death and Other SAEs:	**PBO (N=70)**	**LEV 1000 mg (N=72)**	**LEV 3000 mg (N=71)**
Subjects with SAEs, n (%):	1 (1.4)	5 (6.9)	1 (1.4)
Primary System Organ Class	*n (%) [n considered at drug-related by the Investigator]*		
Injury, poisoning and procedural complications	1 (1.4) [0]	2 (2.8) [2]	1 (1.4) [0]
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.4) [1]	0
Nervous system disorders	0	1 (1.4) [1]	0
Reproductive system and breast disorders	0	1 (1.4) [1]	0

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Primary Outcomes:
Median (Q1-Q3) seizure frequency per week decreased from 3.58 (1.75 - 5.76) at baseline to 2.25 (1.04 - 5.38) over the evaluation for the LEV 1000 mg group and from 3.44 (1.93 - 6.63) to 2.08 (1.21 - 6.57) for the LEV 3000 mg group while medians were similar at baseline (2.73 [1.99 - 5.38]) and over the evaluation (2.67 [1.50 - 5.39]) for the PBO group. For the primary efficacy analysis on the FAS population in the ANCOVA, the estimated percentage reduction (95% confidence interval [CI]) over PBO in the partial onset seizure frequency per week over the evaluation period was 20.9 [10.2%, 30.4%] for the pooling of both LEV groups ($p < 0.001$). When considering the 2 doses of LEV separately, the percentage reduction over PBO [95% CI] in partial onset seizure frequency per week was estimated to 18.8% [6.0%, 29.9%] for LEV 1000 mg ($p = 0.006$) and 23.0% [10.7%, 33.6%] for LEV 3000 mg ($p < 0.001$).

Partial Seizure Frequency per Week	**PBO (N=65)**[(c)]	**LEV 1000 mg (N=64)** [(c)]	**LEV 3000 mg (N=63)** [(c)]
Baseline, median (Q1 - Q3)	2.73 (1.99-5.38)	3.58 (1.75-5.76)	3.44 (1.93-6.63)
Evaluation, median (Q1 - Q3)	2.67 (1.50-5.39)	2.25 (1.04-5.38)	2.08 (1.21-6.57)
Least Square Means	1.563	1.354	1.302
% Reduction over PBO [95% CI]		18.8 [6.0, 29.9]	23.0 [10.7, 33.6]
p-value		0.006	<0.001

[(c)] Subjects with values at both baseline and evaluation periods were taken into account.

Publication Reference(s) based on the study: Murasaki et al., Asian and Oceanian Epilepsy Congress, Malaysia, 2006

Date of report: 06-Mar-2008