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Clinical Study Summary

CT Registry ID#: NCT00280696
Study No.: N01221

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Based on Clinical Study Report document reference code: RRCE07D0208

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

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

Title of Study:
A double-blind, randomized, placebo-controlled 5 parallel groups, confirmatory trial on the efficacy and safety of Levetiracetam used as add-on therapy at doses of 0.5 to 3g/day in patients from 16 to 65 years with epilepsy with partial onset seizures under treatment with 1 to 3 anti-epileptic drug(s)

Investigator(s) (number only): 63

Study Center(s) (number only): 55

Length of Study:
Date first patient enrolled: 15 Nov 2005
Date last patient completed: 07 Nov 2007

Phase of Development: Phase 3 / Confirmatory

Abstract:
The objective of this study was to confirm the efficacy of levetiracetam (LEV) at 1 and 3g/day in reducing seizure frequency in Japanese patients with partial epilepsy not fully controlled despite treatment with 1 to 3 concomitant anti-epileptic drugs as well as to evaluate the efficacy of LEV at doses of 0.5g and 2g/day compared to placebo treatment. The primary efficacy variable was the percentage reduction from Baseline in partial (Type I) seizure frequency per week over the Evaluation Period. One of the secondary efficacy variables was the partial (Type I) seizures frequency per week in partial seizures over the Evaluation Period. Safety assessments included monitoring adverse events, vital signs, laboratory test values, and ECGs.

The analysis on the primary efficacy variable to confirm the efficacy of LEV 1g and LEV 3g was performed using a closed testing procedure which controlled the Type I error rate at 5%, 2-sided. The procedure consisted of the three following steps:

1) A comparison of PBO, LEV 1g, and LEV 3g using the Kruskal-Wallis test at 5% 2-sided significance level.
2) A comparison of PBO and LEV 1g using the Wilcoxon rank-sum test at 5% 2-sided significance level.
3) A comparison of PBO and LEV 3g using the Wilcoxon rank-sum test at 5% 2-sided significance level.

The evaluation of the efficacy of LEV 0.5g and LEV 2 g was performed for each comparison independently using a Wilcoxon rank-sum test at 5% 2-sided significance level.

Subjects included were 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 LEV 0.5g, LEV 1g, LEV 2g, LEV 3g 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 4-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, excluding subjects having major non-compliance with the protocol or Good Clinical Practice.

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Number of Patients	**Placebo**	**L059 0.5g**	**L059 1g**	**L059 2g**	**L059 3g**
Planned, N:			352		
Enrolled, N:	70	72	70	70	70
FAS	70	71*	70	70	70
Completed, n (%):	67 (95.7)	62 (87.3)	64 (91.4)	63 (90.0)	60 (85.7)
Number of Patients Withdrawn, n (%):	3 (4.3)	9 (12.7)	6 (8.6)	7 (10.0)	10 (14.3)
Withdrawn due to Adverse Events, n (%):	1 (1.4)	2 (2.8)	1 (1.4)	4 (5.7)	6 (8.6)
Withdrawn due to lack of efficacy, n (%):	0	0	2 (2.9)	1 (1.4)	1 (1.4)
Withdrawn due to protocol violation, n (%)	1 (1.4)	5 (7.0)	2 (2.9)	1 (1.4)	3 (4.3)
Withdrawn due to lost to follow-up, n (%)	0	0	0	1 (1.4)	0
Withdrawal of consent for personal reasons not related to AEs or lack of efficacy, n (%)	1 (1.4)	1 (1.4)	1 (1.4)	0	0
Withdrawn for Other Reasons, n (%):	0	1 (1.4)	0	0	0
Demography:					
Gender (Females/Males):	35/35	36/35	41/29	35/35	33/37
Age (years), mean(SD):	34.89 (12.56)	33.21 (10.64)	32.80 (10.90)	30.44 (10.06)	33.09 (11.72)
Race, n(%): Asian					
Japanese	69 (98.6)	71 (100.0)	70 (100.0)	70 (100.0)	70 (100.0)
Other Asian	1 (1.4)	0	0	0	0

*Due to major non-compliance with the protocol, one subject who was randomized to L059 0.5 g Group was totally excluded from the FAS.

Primary Outcome:
The primary endpoint was the percentage reduction in partial seizure frequency per week over the Evaluation Period from Baseline. Median (Q1 – Q3) of the primary endpoint on the FAS population were equal to 12.50% (-5.81% – 31.25%) for the PBO group versus 12.92% (-13.56% – 41.89%) in the LEV 0.5g group, 18.00 %(-12.25 %– 39.91%) in the LEV 1g group, 11.11% (-19.64 %– 39.09%) in the LEV 2g group and 31.67% (0.00% – 52.07%) in the LEV 3g group. The comparison of the LEV 1g, LEV 3g, and placebo groups did not show a statistically significant difference (p=0.067) and the closed-testing procedure was stopped. The testing of the 2 remaining comparisons, which was performed using the Wilcoxon rank-sum tests, are purely indicative. Median difference versus placebo (95% CI) has been estimated to 2.27% (-9.23%, 14.44%) for the LEV 1g group (p-value=0.700) and to 14.93% (1.98%, 27.64%) for the LEV 3g group (p-value=0.025). The comparison of the LEV 0.5g group with the placebo group, and LEV 2g group with placebo group did not show statistically significant difference (p=0.918 and p=0.745 respectively). As a result, the primary endpoint did not validate the evidence of the efficacy of daily LEV doses investigated in this study. However, the statistically significant difference observed between LEV 3g and placebo groups suggested the efficacy of the LEV treatment.

The seizure frequency per week in partial seizures over the Evaluation Period showed a trend similar to the primary endpoint.

Safety Outcomes:
During the Treatment Period (Up-Titration + Evaluation), the incidence of Treatment-Emergent Adverse Event (TEAE) did not indicate marked differences between the Placebo and LEV groups. The incidence of at least 1 TEAE in the Placebo, LEV 0.5g, 1g, 2g, and 3g groups was reported at a rate of 81.4%, 78.9%, 81.4%, 75.7%, and 78.6%, respectively. The TEAEs considered to be 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 the Placebo, LEV 0.5g, 1g, 2g, and 3g groups were 58.6%, 60.6%, 61.4%, 58.6%, and 64.3%, respectively. In the treatment

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period, 14 subjects were discontinued from the study due to AEs. The number of discontinued subjects in the PBO, LEV 0.5g, 1g, 2g, and 3g groups was 1, 3, 1, 4, and 5, respectively. In the treatment period, 12 subjects reported treatment-emergent SAEs. The number of subjects reported with SAEs in the PBO, LEV 0.5g, 1g, 2g, and 3g groups were 3, 2, 2, 1, and 4, respectively. There was 1 fatal event due to gastric cancer with an unlikely relationship to LEV, which was reported during the post-study period. The TEAEs and Serious AEs reported by primary system organ class at least 10% of subjects in any of the treatment groups are shown below.

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

Treatment Emergent AEs (TEAE) during Up-Titration + Evaluation- Safety Population

	Placebo	**L059 0.5g**	**L059 1g**	**L059 2g**	**L059 3g**
Patients with at least one TEAE, n(%):	57 (81.4)	56 (78.9)	57 (81.4)	53 (75.7)	55 (78.6)
Patients with TEAEs (by Primary System Organ Class)	*n (%) [n considered drug-related by the Investigator]*				
Gastrointestinal disorders	22 (31.4) [19]	15 (21.1) [13]	11 (15.7)[10]	7 (10.0) [6]	11 (15.7) [7]
General disorders and administration site conditions	5 (7.1) [5]	5 (7.0) [4]	2 (2.9) [1]	3 (4.3) [2]	7 (10.0) [6]
Infections and infestations	21 (30.0)[9]	23 (32.4) [13]	30 (42.9) [18]	29 (41.4) [16]	27 (38.6) [17]
Injury, poisoning and procedural complications	17 (24.3) [6]	18 (25.4) [8]	13 (18.6) [3]	17 (24.3) [6]	18 (25.7) [7]
Investigations	8 (11.4) [8]	8 (11.3) [7]	6 (8.6) [6]	5 (7.1) [4]	11 (15.7) [9]
Nervous system disorders	19 (27.1) [16]	16 (22.5) [15]	13 (18.6) [11]	18 (25.7) [17]	23 (32.9) [21]
Respiratory, thoracic and mediastinal disorders	8 (11.4) [6]	8 (11.3) [5]	4 (5.7) [3]	9 (12.9) [5]	7 (10.0) [3]
Death, SAEs, and Other SAEs during Up-Titration + Evaluation- Safety Population					
Death, n (%):	0	0	0	0	1 (1.4)*
Patients with SAEs, n(%):	3(4.3)	2 (2.8)	2 (2.9)	1 (1.4)	4 (5.7)
Patients with SAEs (by Primary System Organ Class)	*n(%) [n considered drug-related by the Investigator]*				
Cardiac disorders	0	0	1(1.4) [1]	0	0
Infections and infestations	0	1(1.4) [0]	0	0	0
Injury, poisoning and procedural complications	2 (2.9) [1]	0	1(1.4)[0]	0	1(1.4) [1]
Neoplasms benign, malignant and unspecified	0	0	0	0	1(1.4) [1]
Nervous system disorders	1 (1.4) [1]	1(1.4) [1]	0	1(1.4) [1]	1(1.4) [0]
Psychiatric disorders	0	0	0	0	1(1.4) [1]

*This fatal event, gastric cancer was reported during the post-study period.

Publication Reference(s) based on the study: None

Date of report: 14-Nov-2008