UCB reference No.: RXCE08H2201

Approved by UCB 08 Oct 2008

Clinical Study Summary

CT Registry ID#: NCT00175903
Study No.: N01175

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Based on clinical study report document reference code: RRCE07J0701

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

Name of Sponsor/Company: UCB Pharma SA

Title of study:
A therapeutic confirmatory, open-label, multicenter, randomized 2-parallel groups, community-based trial studying the efficacy and safety of levetiracetam (1000 to 3000mg/day oral tablets 250-500mg bid) compared to sodium valproate (1000 to 2000mg/day oral ER tablets 300-500mg bid) and carbamazepine (600 to 1600mg/day oral CR tablets 200-400mg bid) as monotherapy in subjects with newly diagnosed epilepsy.

Investigator(s) (number only): 269

Study center(s) (number only): 269

Length of study:
Date first patient enrolled: 09 Feb 2005
Date last patient completed: 13 Oct 2007

Phase of development: Phase 3b/Therapeutic confirmatory

Abstract:
The primary objective of this study was to assess the effectiveness of levetiracetam (LEV) in monotherapy compared to 2 principal older antiepileptic drugs (AEDs) (sodium valproate extended release [VPA-ER] or carbamazepine controlled release [CBZ-CR]) as a group (older AEDs).

The primary effectiveness variable was the time to withdrawal from study medication (counted from the first day of study drug administration) as a measure of combined efficacy and safety. The primary efficacy variable was analyzed using Cox's proportional hazards regression model for the intent-to-treat (ITT) population.

The secondary efficacy variables:
Effectiveness: the time to withdrawal comparing LEV versus the older AEDs based on the subset of subjects whose best recommended treatment was CBZ-CR or VPA-ER; the retention rate after 6 and 12 months comparing LEV versus the older AEDs, and LEV versus older AEDs based on the subset of subjects whose best recommended treatment was CBZ-CR or VPA-ER.

Efficacy: seizure freedom at 6 and 12 months; time to first seizure, both comparing LEV versus older AEDs as a group and LEV versus the subset of subjects whose best recommended treatment was CBZ-CR or VPA-ER.

Methodology: The treatment effect (hazard ratio) was described using 2-sided 95% confidence intervals (CI). The time to withdrawal was analyzed using a Cox's proportional hazards regression model for the ITT population for each of the best recommended treatment subsets. The retention rate after 6 and 12 months was analyzed using a logistic regression model for the ITT population for LEV versus older AEDs and for each of the best treatment subsets. Seizure freedom at 6 and 12 months and time to first seizure was analyzed using a Cox's proportional hazards regression model for the ITT population for LEV versus older AEDs and for each of the best recommended treatment subsets. The time to first seizure for LEV versus older AEDs and the time to first seizure excluding up-titration for LEV versus older AEDs were analyzed by Cox's proportional hazard regression and Kaplan-Meier survival analysis as described for the primary efficacy analysis and under the same conditions, for the ITT population with safety treatment and per protocol populations.

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Safety assessments included the monitoring of adverse events (AEs), physical and neurological examinations, vital signs, and body weight.
Subjects were to be male or female, age ≥16 years if permitted by law, otherwise ≥18 years, with a diagnosis of epilepsy (all types of seizures could be included) during the past year, had at least 2 unprovoked seizures in the past 2 years with at least 1 during the last 6 months, and had no previous exposure to LEV, VPA-ER, or CBZ-CR. They were permitted to have been treated with a rescue medication (eg, lorazepam, diazepam) before and also have had a maximum of 2 weeks exposure to another antiepileptic treatment (except LEV, CBZ or VPA).

After randomization, the subject entered a 2-week up-titration period until the target dose was reached (LEV: 1000mg/day, CBZ-CR: 600mg/day, VPA-ER: 1000mg/day). The target dose was maintained during the remainder of the study unless a seizure occurred and further up-titration was considered necessary by the Investigator (maximum dose: LEV: 3000mg/day, CBZ-CR: 1600mg/day, VPA-ER: 2000mg/day). In case a subject did not tolerate a dose increase, he/she had the opportunity to fallback to a lower dose but not below the target dose, and to continue in the study on that basis. The duration of treatment was a maximum of 60 weeks except in Germany (maximum 60 weeks for CBZ and VPA subjects; until LEV has been granted a monotherapy indication in Germany for LEV subjects).

Number of subjects:	**Old AEDs**	**LEV**
Planned, N	982	982
Randomized, N	856[a]	843[a]
ITT population, N	847	841
Completed, n (%)	627 (74.0)	639 (76.0)
Number of subjects withdrawn, n (%)	220 (26.0)	202 (24.0)
Withdrawn due to AEs, n (%)	110 (13.0)	71 (8.4)
Withdrawn due to lack of efficacy, n (%)	25 (3.0)	35 (4.2)
Withdrawn due to lost to follow-up, n (%)	34 (4.0)	36 (4.3)
Withdrawal of consent for personal reasons not related to AEs or lack of efficacy, n (%)	36 (4.3)	38 (4.5)
Withdrawn for other reasons, n (%)	15 (1.8)	22 (2.6)

[a] Two subjects were treated without being randomized: 1 subject received old AED and 1 subject LEV. In addition, 2 subject identifiers were in fact for the same subject who had filledin 2 separate CRFs (only Visit 1 data were doubled).

Demography:	**Old AEDs**	**LEV**
Gender (Females/males)	371/476	375/466
Age (years), mean (SD)	40.84 (17.80)	40.61 (17.76)
Race, n (%)		
Caucasian	826 (97.5)	818 (97.3)
African-American	5 (0.6)	8 (1.0)
Asian/Pacific Islander	6 (0.7)	8 (1.0)
Hispanic	5 (0.6)	2 (0.2)
Indian/Pakistani	2 (0.2)	3 (0.4)
Other/mixed race	3 (0.4)	2 (0.2)

Primary outcomes:
The study showed no clear superiority of LEV over old AEDs on the primary variable, with a hazard ratio [95% CI] of 0.90 [0.74–1.08] slightly in favor of LEV and a p-value for the treatment difference of 0.258.

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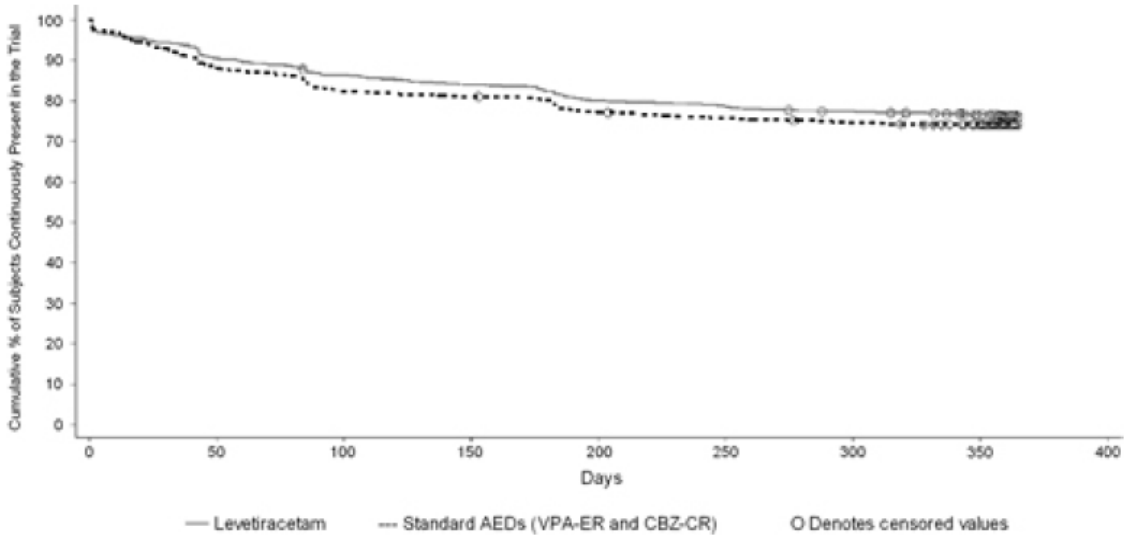

Secondary outcomes:
Time to withdrawal was not significantly different between groups when analyzed by strata: hazard ratios [95% CI] i) LEV/VPA-ER (349/347) 1.02 [0.74-1.41]; ii) LEV/CBZ-CR (492/500) 0.84 [0.66-1.07].

No difference was observed for the retention rate at 6 months, with an odds ratio [95% CI] for LEV over older AEDs of 1.157 [0.906-1.477] and a p-value of 0.242. Similarly, no difference was observed for the retention rate at 12 months, with an odds ratio [95% CI] for LEV over older AEDs of 1.155 [0.954-1.400] and a p-value of 0.140. A similar absence of statistically significant treatment difference was observed when evaluating the retention rate within each strata of best recommended treatment.

The seizure-freedom rates observed at 6 months showed no difference, with an odds ratio [95% CI] for LEV over old AEDs of 0.927 [0.765-1.124] and a p-value of 0.441. Similarly, no difference was observed at 12 months, with an odds ratio [95% CI) for LEV over old AEDs of 1.087 [0.876-1.349] and a p-value of 0.447.

The time to first seizure analysis resulted in a p-value of 0.022 when comparing LEV and the older AEDs, in favor of the older AEDs group: the hazard ratio [95% CI] was 1.20 [1.03-1.39].
The same tendency favoring CBZ-CR and VPA-ER over LEV was observed when evaluating the time to first seizure within each best recommended treatment strata, although the differences were not statistically significant:

- LEV over CBZ-CR: hazard ratio [95% CI] of 1.20 [0.99-1.46] and p-value of 0.061
- LEV over VPA-ER: hazard ratio [95% CI] of 1.19 [0.93-1.54] and p-value of 0.167

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Safety outcomes:
Number (%) of subjects with treatment-emergent AEs (preferred terms) that represented at least 5% in any of the treatment groups by MedDRA preferred term – safety population

UCB system organ class Preferred term	CBZ-CR N=499 n (%)	VPA-ER N=342 n (%)	Older AEDs N=841 n (%)	LEV N=835 n (%)
Vertigo	25 (5.0)	11 (3.2)	36 (4.3)	40 (4.8)
Diarrhoea	20 (4.0)	19 (5.6)	39 (4.6)	38 (4.6)
Nausea	39 (7.8)	18 (5.3)	57 (6.8)	44 (5.3)
Fatigue	95 (19.0)	39 (11.4)	134 (15.9)	120 (14.4)
Nasopharyngitis	32 (6.4)	14 (4.1)	46 (5.5)	40 (4.8)
Weight increased	33 (6.6)	65 (19.0)	98 (11.7)	47 (5.6)
Headache	112 (22.4)	58 (17.0)	170 (20.2)	161 (19.3)
Tremor	11 (2.2)	32 (9.4)	43 (5.1)	14 (1.7)
Dizziness	52 (10.4)	18 (5.3)	70 (8.3)	68 (8.1)
Somnolence	35 (7.0)	13 (3.8)	48 (5.7)	68 (8.1)
Depression	13 (2.6)	7 (2.0)	20 (2.4)	43 (5.1)
Alopecia	5 (1.0)	18 (5.3)	23 (2.7)	11 (1.3)
Rash	29 (5.8)	0	29 (3.4)	9 (1.1)

%: denominator=N by treatment

There were less subjects on LEV (8.4%) than on the standard AEDs (13.0%) that were withdrawn from the study primarily due to AEs (p=0.0025). Adverse events leading to permanent study drug discontinuation were reported most frequently in the CBZ-CR group (8.8%) and least frequently in the VPA-ER group (4.7%).

Nine deaths were reported during the study, of which 2 (0.4%) in the CBZ-CR group, 1 (0.3%) in the VPA-ER group, and 5 (0.6%) in the LEV group were treatment-emergent. In the CBZ-CR group, 1 subject died as as a result of subarachnoid haemorrhage, and 1 subject from acute myocardial infarction. In the VPA-ER group, 1 subject died a sudden unexplained death in epilepsy. In the LEV group, 1 subject died of bilateral pulmonary embolism prior to the planned first intake the same day. Two subjects died from the consequences of brain neoplasms. One subject was suspected to have died from cardiac arrhythmia (asystolia). One subject died from cerebral hematoma and subdural hemorrhage due to a head injury during a traffic accident. One subject died from injuries related to radionecrosis, 2 years after the last dose of LEV.

Publication reference(s) based on the study:

Pohlmann-Eden E, Van Paesschen W, Hallström Y, et al. The KOMET study: an open-label, randomized, parallel-group trial comparing the efficacy and safety of levetiracetam with sodium valproate and carbamazepine as monotherapy in subjects with newly diagnosed epilepsy. 62nd Annual Meeting of the American epilepsy society, Seattle, WA, USA, 5 to 9 Dec 2008, Abstract 3.242.

Trinka E, Van Paesschen W, Hallström Y, et al. The KOMET study: an open-label, randomized, parallel-group trial comparing the efficacy and safety of levetiracetam with sodium valproate and carbamazepine as monotherapy in subjects with newly diagnosed epilepsy. Abstract Book, 8th European Congress of Epileptology, Berlin, Germany, 21 to 25 Sep 2008:50, 006.

Date of report: 08 Oct 2008