Epilepsy & Behavior 97 (2019) 67–74

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

A randomized, open-label, multicenter comparative trial of levetiracetam and topiramate as adjunctive treatment for patients with focal epilepsy in Korea

Sang Kun Lee [a,1], Sang Ahm Lee [b,1], Dong Wook Kim [c], Christian Loesch [d], Barbara Pelgrims [e], Toru Osakabe [f], Byungin Lee [g,*], on behalf of the N01353 study group

[a] Seoul National University Hospital, Seoul, Republic of Korea
[b] University of Ulsan College of Medicine, Seoul, Republic of Korea
[c] Department of Neurology, Konkuk University School of Medicine, Seoul, Republic of Korea
[d] UCB Pharma, Monheim, Germany
[e] UCB Pharma, Brussels, Belgium
[f] UCB Pharma, Tokyo, Japan
[g] Injie University Haeundae Paik Hospital, Busan, Republic of Korea

ARTICLE INFO

Article history:
Received 19 April 2019
Revised 15 May 2019
Accepted 16 May 2019
Available online 10 June 2019

Keywords:
Partial-onset seizures
Antiepileptic drugs
Add-on

ABSTRACT

Objective: The objective of this trial was to compare the effectiveness of levetiracetam (LEV) and topiramate (TPM) as adjunctive treatment for patients with focal seizures in Korea.
Methods: In this Phase IV, open-label, multicenter trial (NCT01229735), adults were randomized to treatment with LEV (1000–3000 mg/day) or TPM (200–400 mg/day). Only patients achieving LEV ≥1000 mg/day or TPM ≥100 mg/day after a 4-week up-titration entered the 20-week dose-finding and subsequent 28-week maintenance periods. The primary outcome was the 52-week retention rate; others included safety and exploratory efficacy outcomes.
Results: Of 343 randomized patients (LEV 177; TPM 166), 211 (61.5%) completed the trial. In the full analysis set (FAS), retention rate was 59.1% with LEV vs 56.6% with TPM ($p = 0.7007$), while in the prespecified sensitivity analysis, based on data from patients who received drug doses in the recommended range (LEV 176; TPM 113), it was 59.1% with LEV vs 42.5% with TPM ($p = 0.0086$). In the FAS, median percent reduction in seizure frequency from baseline was 74.47% with LEV and 67.86% with TPM ($p = 0.0665$); ≥50% responder rate was 69.0% vs 64.8% ($p = 0.4205$), and the 6-month seizure-freedom rate was 35.8% vs 22.3% ($p = 0.0061$). In the sensitivity analysis, differences between groups were greater, favoring LEV. Incidences of treatment-emergent adverse events (TEAEs) were 70.6% with LEV vs 77.1% with TPM; most frequently somnolence (20.3%), dizziness (18.1%), and nasopharyngitis (13.6%) with LEV; and decreased appetite (15.7%), dizziness (14.5%), and headache (14.5%) with TPM. Discontinuations due to TEAEs were 7.9% with LEV and 12.7% with TPM.
Conclusions: In this open-label trial, the 52-week retention rate was not significantly different between LEV and TPM. However, LEV was associated with a substantially higher seizure freedom rate and a more favorable safety profile than TPM in this population of Korean patients with focal seizures.

1. Introduction

The antiepileptic drugs (AEDs) levetiracetam (LEV) and topiramate (TPM) are both commonly prescribed for the treatment of patients with epilepsy worldwide. The use of both drugs as adjunctive therapy for patients with focal seizures has been evaluated in clinical trials in South Korea, where they have been shown to be efficacious [1–4].

Data from retrospective studies, reflecting the use of these AEDs in routine clinical practice, are also available. One such study included a direct comparison between LEV and TPM in the treatment of patients with predominantly drug-resistant focal epilepsy [5]. In this single-center Dutch study, LEV was shown to be associated with significantly greater retention at 1 year than TPM (65.6% vs 51.7%, $p = 0.0015$). In other single-center studies, the effectiveness of multiple AEDs, including LEV and TPM, was compared; in a US study, the 2-year retention rate was higher among LEV- than TPM-treated patients, while in a Finnish study, the 3-year retention rate of both AEDs was similar [6,7]. In a more recent Finnish study, which only included patients with drug-resistant focal epilepsy, 3-year retention rates were again similar [8]. In Korea,

* Corresponding author at: Department of Neurology, Inje University College of Medicine, Haeundae Paik Hospital, 875 Haeundae-ro, Haeundae-gu, Busan 48108, Korea.
E-mail address: bilee@paik.ac.kr (B. Lee).
[1] Colead authors.

https://doi.org/10.1016/j.yebeh.2019.05.014
1525-5050/

specifically, a recent single-center analysis of data from patients attending the Seoul National University Hospital showed that 3-year retention rates were similar among patients with focal or generalized seizures treated with LEV or TPM [9]. It was notable that mean daily doses in this Korean study were below the recommended 1200 mg and 200 mg for LEV and TPM, respectively.

Given the limitations inherent to retrospective studies, as well as potentially different dosages required for Korean patients, a prospective, randomized trial was conducted with the objective of comparing long-term use of LEV and TPM as adjunctive therapy for patients with focal epilepsy in Korea. The primary outcome of the trial was the 52-week retention rate. Retention, a reflection of clinical effectiveness, combines efficacy and tolerability and has been described as a measure of a patient's willingness to take a drug [10]. Importantly, retention data provide information that can be applied readily to everyday practice [10].

2. Methods

N01353 (NCT01229735) was a Phase IV, open-label, randomized, parallel group, multicenter trial conducted across 24 centers in South Korea from November 2010 to May 2015.

Informed consent was obtained from patients, or legal guardians, before enrollment. The trial protocol, amendments and patient informed consent were reviewed by national and local Independent Ethics Committees and Institutional Review Boards. The trial was conducted in accordance with all applicable local regulations, the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) requirements, and the ethical principles founded in the Declaration of Helsinki.

2.1. Patient population

Patients were eligible for enrollment if they were aged 16–80 years (inclusive), had a confirmed diagnosis of epilepsy and were experiencing focal seizures despite treatment with 1–3 concomitant AEDs, taken at stable and optimal dosages for ≥4 weeks before Visit 1 and the 4 weeks before Visit 2 (Fig. 1). Patients must have experienced ≥2 focal seizures, with or without bilateral tonic-clonic seizures (secondarily generalized), during the 8-week retrospective baseline and ≥1 focal seizure during the 4-week prospective baseline period. The longest interval between seizures during the 12-week baseline period must have been <6 weeks. Exclusion criteria included previous treatment with LEV or TPM, history of psychogenic or cluster seizures, status epilepticus in the preceding 3 months, alcohol or drug abuse, or suicidality. Patients were also excluded if they had exclusively focal aware nonmotor (simple focal nonmotor) seizures, any generalized epilepsies, or any sign suggestive of a rapidly progressing neurological disease. Female patients of childbearing potential were required to use contraception.

2.2. Randomization and blinding

Patients were randomized 1:1 using the Interactive Web Response System. The randomization code was generated using fixed blocks by an independent statistician who was not otherwise involved in the trial. Randomization was stratified according to trial centers. Since the trial had an open-label design, blinding was not required.

2.3. Trial design and procedures

Patients entered a 4-week prospective baseline period, preceded by an 8-week retrospective baseline (Fig. 1). The combined 12-week baseline was followed by a 52-week treatment period that consisted of a 4-week titration, 20-week dose-finding, and 28-week maintenance periods. At the end of the treatment period, patients had the option of continuing or stopping their allocated treatment. If a patient opted to stop treatment at trial end, or at any time during the trial, he/she entered a down-titration period.

Dosage and titration schedules were determined in accordance with local product labels. In the up-titration period, patients randomized to LEV started on 500 mg/day, which was increased to 1000 mg/day after 2 weeks; TPM was initiated at 25 mg/day (administered once daily) and increased weekly in 25-mg increments to 100 mg/day. Patients who did not achieve daily dosages of LEV ≥1000 mg or TPM 100 mg at the end of the up-titration period were withdrawn. During dose-finding, dosages were adjusted by the investigator to a maximum of LEV 3000 mg/day or TPM 400 mg/day, according to individual patient combined efficacy and tolerability responses. Patients entered the maintenance period continuing on their last dosage at the end of the dose-finding period. During maintenance, a single dosage change was permitted at the investigator's discretion. The recommended effective dosages during maintenance were 1000–3000 mg/day for LEV and 200–400 mg/day for TPM, in accordance with drug labeling in Korea. However, based on the results of a Korean study that reported median TPM dose 100 mg/day and 200 mg/day after 3 months and 1 year of treatment, respectively, use of TPM 100 mg/day was permitted [11]. Concomitant AEDs were to be kept at stable dosages throughout the treatment period.

2.4. Trial outcomes

The primary outcome was the 52-week retention rate, defined as the percentage of patients continuing their allocated treatment from the first administration for 52 weeks.

Standard efficacy outcomes were assessed based on data obtained from the 52-week visit and included median percent reduction from baseline in weekly focal seizure frequency and ≥50% responder rate, defined as patients with ≥50% reduction in weekly focal seizure frequency from baseline. Baseline seizure frequency was determined by the

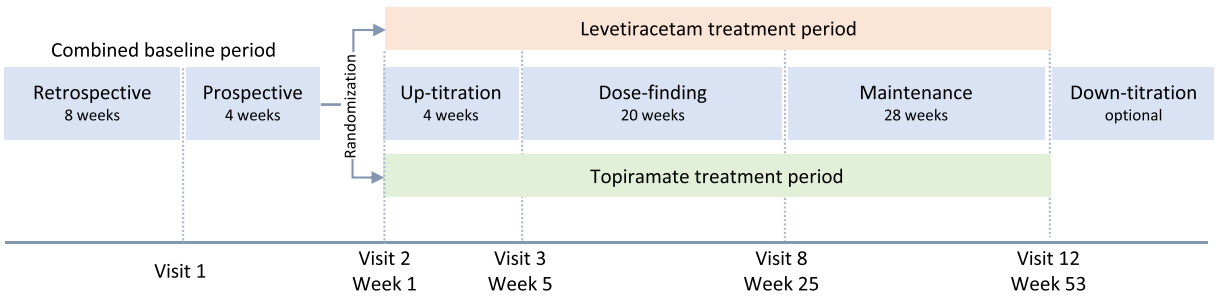

Fig. 1. Trial design. After a 12-week combined baseline period, patients were randomized 1:1 to receive treatment with levetiracetam or topiramate over a period of 52 weeks.

number of daily seizures recorded by patients in their daily record card during the 4-week prospective baseline period. The 6-month seizure freedom rate, occurring in any consecutive 6-month timespan during the treatment period, was also assessed.

Safety and tolerability outcomes included the incidence of treatment-emergent adverse events (TEAEs), drug discontinuations due to TEAEs, standard laboratory tests, electrocardiogram, and physical and neurological examinations.

2.5. Statistical analysis

A sample size of 170 patients per arm was calculated to achieve 80% power at a 5% significance level, using a Pearson chi-square two-sided test for difference in 52-week retention rates in the LEV and TPM groups, when assuming an absolute difference between LEV and TPM of 15%.

The primary outcome was analyzed using logistic regression modeling of 52-week retention by treatment and center pooling category (North Seoul, South Seoul or outside Seoul). p-Values were calculated for the likelihood ratio test of the treatment group regression coefficient against 0. Confidence intervals (CIs) for odds ratios (ORs) were the 95% profile likelihood CIs. For efficacy outcomes, percent reduction from baseline in weekly focal seizure frequency during the treatment period was evaluated using the Wilcoxon rank sum test, while the ≥50% responder rate (across the whole treatment period) and 6-month seizure freedom rate (at any time during the treatment period) were evaluated using the Pearson chi-square test. A significance level of 5% was used for statistical testing; however, all corresponding p-values for the efficacy outcomes were considered exploratory. Analyses of the primary and efficacy outcomes were based on the full analysis set (FAS), which included all randomized patients who received ≥1 dose of trial drug (safety set; SS) and had ≥1 postbaseline seizure diary entry.

Two further sets of analysis were conducted. A protocol-specified sensitivity analysis was conducted using data from patients who were prescribed trial drugs within the recommended dosage range (1000–3000 mg/day for LEV and 200–400 mg/day for TPM) during the maintenance period (sensitivity subgroup). Patients in the FAS who were prescribed dosages outside of the recommended range, starting at any visit during, and continuing to the end of their individual maintenance period, were excluded from the sensitivity subgroup. A posthoc analysis was conducted using data from two subgroups of patients from the FAS in each treatment arm based on the observed mean daily dose during their combined dose-finding and maintenance period. The first was the low-dose subgroup (<1500 mg/day LEV, <200 mg/day TPM), and correspondingly, the second was the high-dose subgroup (≥1500 mg/day LEV, ≥200 mg/day TPM). The dose-finding period was included to reflect real-life clinical practice more closely, and the subgroup dose cutoffs – 1500 mg/day for LEV and 200 mg/day for TPM – were selected as they each represent half of the highest recommended dose for adjunctive treatment of patients with focal seizures [12,13]. It is important to note that the sensitivity analysis was based on data from the investigator prescription records, whereas the posthoc analysis was based on data from actually observed intake records. Statistical testing for the subgroups identified in the sensitivity and posthoc analyses was conducted in a similar manner to the primary outcome; however, all p-values were considered exploratory.

3. Results

3.1. Patients

A total of 343 patients were randomized to treatment with LEV (n = 177), or TPM (n = 166); 211 (61.5%) completed the trial (Fig. 2). In the LEV group, all 177 patients received ≥1 dose of trial drug (SS), and 176 also had ≥1 efficacy assessment (FAS). In the TPM group, both the SS and the FAS consisted of 166 patients.

All LEV-treated patients met the requirements for inclusion in the sensitivity subgroup; therefore, the subgroup was identical to patients in the FAS (n = 176). In contrast, 53 TPM-treated patients group had to be excluded, leaving 113 patients in the sensitivity subgroup. For the posthoc analysis, the LEV group consisted of 161 of 177 patients, of whom 100 were included in the low- and 61 in the high-dose subgroups; 16 patients who did not enter the dose-finding period could not be assigned to either subgroup. Correspondingly, the TPM group consisted of 153 of 166 patients, of whom 117 were included in the low- and 36 in the high-dose subgroups; 12 patients who did not enter the dose-finding period, and one who did not have a date for end of TPM administration, could not be assigned to either subgroup.

Median dosages received during the treatment period were 1131.81 mg/day for the LEV SS, 131.32 mg/day for the TPM SS, and 218.44 mg/day for the sensitivity subgroup.

There was a higher proportion of male than female patients in both groups (Table 1). A slightly greater proportion of patients in the LEV group had complex focal seizures at baseline compared with the TPM group; conversely, the TPM group had a slightly greater proportion of patients with focal aware and focal to bilateral seizures (simple focal and secondarily generalized). Patients in both the LEV and TPM lower-dose subgroups had lower baseline seizure frequency than those in the higher-dose subgroups (Table S1). The majority of patients had previously taken and stopped at least one AED, 71.2% in the LEV group and 77.1% in the TPM group. The most commonly used concomitant AEDs in both groups were oxcarbazepine (36.7% and 32.5% in the LEV and TPM groups, respectively), carbamazepine (31.1% and 39.8%), and valproate (26.0% and 24.1%).

3.2. Primary outcome — 52-week retention rate

In the FAS, the 52-week retention rate was numerically greater in patients in the LEV group than in the TPM group, but was not statistically significant (LEV 59.1% vs TPM 56.6%; p = 0.7007, confirmatory), indicating that superiority of LEV over TPM was not established (Table 2). Sensitivity analysis revealed a substantially greater 52-week retention rate for LEV than for TPM (LEV 59.1% vs TPM 42.5%; p = 0.0086, exploratory) (Table 2). In the posthoc analysis, as for the overall population, retention rates in the low- and high-dose subgroups were similar for both treatment groups (Table S2).

3.3. Efficacy outcomes

In the FAS, median percent reduction in seizure frequency during the treatment period was numerically greater among LEV-treated patients compared with TPM-treated patients (74.47% vs 67.86%; p = 0.0665) (Fig. 3A). Similarly, in the FAS, the ≥50% responder rate was numerically higher among LEV-treated compared with TPM-treated patients (69.0% vs 64.8%; p = 0.4205) (Fig. 3B). In the sensitivity analysis, comparisons between the LEV and TPM subgroups revealed greater differences in favor of LEV in median percent reduction in seizure frequency (74.47% vs 52.60%; p = 0.0004) and in the 50% responder rate (69.0% vs 53.6%; p = 0.0085) (Fig. 3A and B). The 6-month seizure freedom rate was higher for the LEV group than the TPM group in the FAS (35.8% vs 22.3%; p = 0.0061) and also in the sensitivity subgroups (35.8% vs 8.8%; p < 0.0001) (Fig. 3C).

In the posthoc analysis, LEV efficacy was substantially greater than that of TPM in the low-dose subgroups, as assessed by median percent reduction in seizure frequency (92.54% vs 72.70%; p < 0.0001), ≥50% responder rate (86.9% vs 69.2%; p = 0.0020), and 6-month seizure-freedom rate (57.0% vs 27.4%; p < 0.0001) during the treatment period (Fig. S1). All p-values are exploratory. In the LEV and TPM high-dose subgroups, slight differences in the efficacy outcomes were in favor of TPM; however, patient numbers were relatively small.

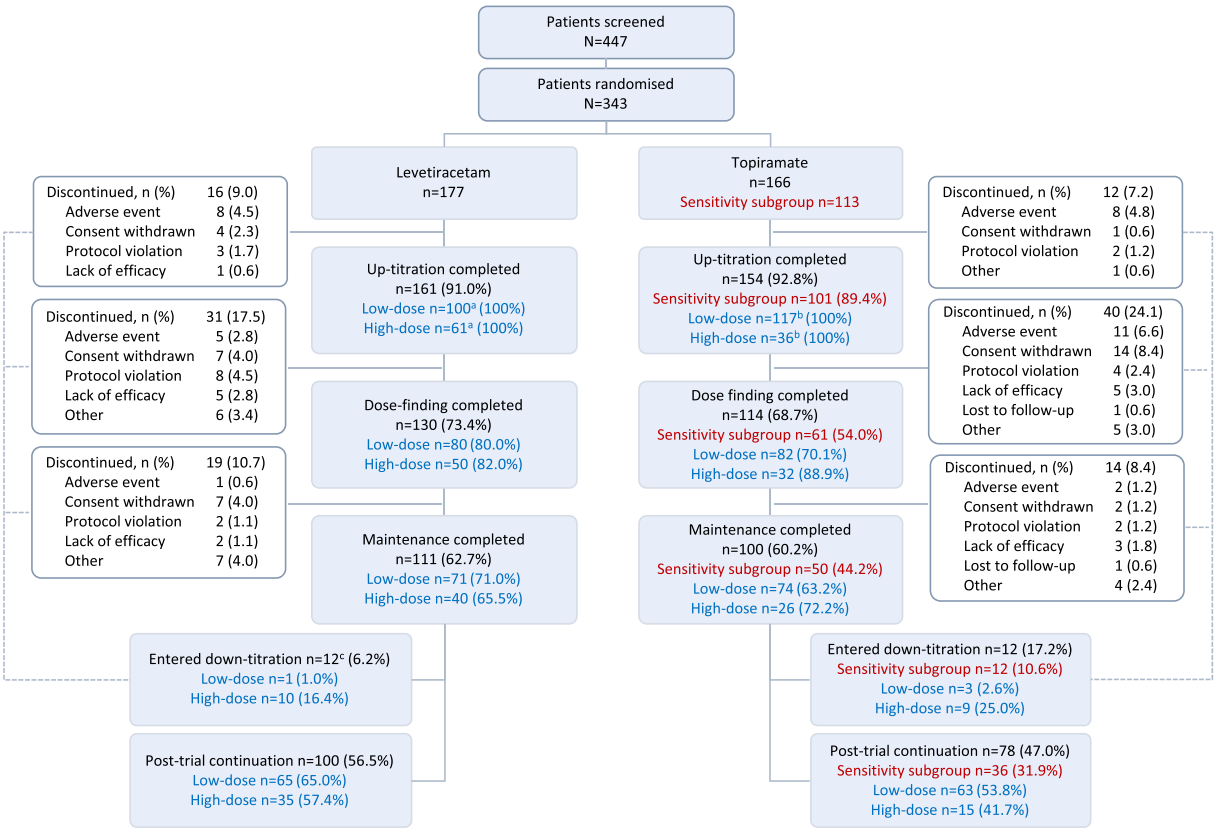

Fig. 2. Patient disposition. For the protocol-specified sensitivity analysis, patient numbers in the topiramate (TPM) sensitivity group are shown in red and include all those who were prescribed TPM doses within the recommended range during the maintenance period. Since all levetiracetam (LEV)-treated patients met the requirements for inclusion in the sensitivity subgroup, the subgroup was identical to the FAS; therefore, separate patient numbers are not provided. For the posthoc analysis, low-dose (LEV <1500 and TPM <200 mg/day) and high-dose (LEV ≥1500 and TPM ≥200 mg/day) subgroups were based on observed mean daily dosage during the combined dose-finding and maintenance period (shown in blue). [a] 16 patients who did not enter the dose-finding period could not be assigned to either subgroup; therefore, 161 of 177 patients were included in the posthoc analysis. [b] 12 patients who did not enter the dose-finding period, and 1 who did not have a date for end of TPM administration could not be assigned to either subgroup. Therefore, 153 of 166 patients were included in the posthoc analysis. [c] One patient discontinued from the up-titration period and directly entered the down-titration period. For inclusion in the low- or high-dose groups of the posthoc analysis, patients were required to have exposure to trial drug during the combined dose-finding/maintenance period; therefore data from that patient were not included. Percentages are based on the randomized set, or randomized sensitivity subset, except for patients excluded before randomization (based on screening set).

3.4. Safety and tolerability

Fewer patients reported TEAEs or discontinued because of TEAEs with LEV than TPM (Table 3). The difference in discontinuations due to TEAEs was even greater in the comparison with TPM sensitivity subgroup (Table 3).

In the low-dose subgroups, the incidence of, and discontinuations due to TEAEs were lower for LEV than TPM (69.0% vs 75.2% and 5.0% vs 11.1%, respectively) (Table S3). In the high-dose subgroups, the incidence of TEAEs was also lower for LEV than TPM (75.4% vs 86.1%), but this was not the case for discontinuations due to TEAEs (1.6% vs 0%) (Table S3).

The three most frequently reported TEAEs were somnolence, dizziness, and nasopharyngitis in the LEV SS; and decreased appetite, dizziness, and headache in the TPM SS and the TPM sensitivity subgroup (Table 3).

4. Discussion

In this randomized, open-label trial, the 52-week retention rate in the FAS was 59.1% with LEV and 56.6% with TPM. Since the difference was not statistically significant, superiority of LEV over TPM was not established. A possible explanation for this result is the use of lower-than-recommended TPM doses in approximately a third of the patients (53/166). Results of the prespecified sensitivity analysis, which included only patients from the FAS who were prescribed dosages in the recommended range during the maintenance period, showed that retention with LEV was substantially higher than with TPM (59.1% vs 42.5%), lending support to this hypothesis.

The recommended dosage range for TPM as adjunctive therapy is 200–400 mg/day [12,14]. In a randomized, double-blind, placebo-controlled trial, the tolerability profile of TPM in the Korean population was found to be different to that in Western populations, with anorexia and gastrointestinal symptoms predominating in Korean patients [3]. In the trial, TPM could be titrated up to 600 mg/day if needed; while most patients (49/78) reached this dosage, the titration schedule was slower than that used in Western trials. In a subsequent trial, use of lower doses and an even more gradual titration schedule resulted in better tolerability and retention [4]. Consequently, in accordance with local clinical practice [11], use of TPM 100 mg/day was permitted in this trial. Patients who achieved acceptable seizure control at the end of the titration period were most likely maintained on this dosage, as there was no clinical rationale to increase it to the recommended range (200–400 mg/day). Indeed, in the initial trial by the Korean Topiramate Study Group, no significant differences in efficacy measures were found in patients taking TPM ≤200 mg/day, >200–≤400 mg/day, or >400–≤600 mg/day [3]. Patients who took recommended TPM doses likely represent a subgroup with greater disease severity, requiring higher doses to achieve seizure control, while also being able to tolerate these higher doses.

This hypothesis is supported by the observations in the posthoc analysis, where patients in the high-dose subgroups had a higher median weekly baseline seizure frequency (LEV 1.30, TPM 0.96) compared with those in the low-dose subgroups (LEV 0.52, TPM 0.75). The posthoc

Table 1
Patient demographics, baseline characteristics, and treatment profile (safety set).

	LEV (n = 177)	TPM (n = 166)	TPM-sensitivity subgroup[a] (n = 113)
Age, mean (SD), years	40.9 (13.6)	39.7 (11.8)	39.8 (12.3)
Male, n (%)	106 (59.9)	102 (61.4)	65 (57.5)
Weight, mean (SD), kg	64.98 (10.60)	66.29 (12.53)	65.32 (12.42)
Age at diagnosis, mean (SD), years	26.0 (15.8)	25.3 (13.6)	25.1 (13.7)
Epilepsy duration, mean (SD), years	15.3 (12.6)	14.9 (12.1)	15.3 (12.5)
Focal seizure history, n (%)[b]			
— Focal aware (simple partial)	22 (12.4)	34 (20.5)	20 (17.7)
— Focal impaired awareness (complex partial)	134 (75.7)	109 (65.7)	75 (66.4)
— Focal to bilateral (secondarily generalized)	100 (56.5)	100 (60.2)	69 (61.1)
History of status epilepticus, n (%)[c]	2 (1.1)	3 (1.8)	3 (2.7)
Baseline weekly focal seizure frequency, median (Q1, Q3)[d]	0.78 (0.48, 1.81)	0.78 (0.47, 1.56)	0.88 (0.52, 1.81)
Number of previous AEDs			
— Mean (SD)	1.3 (1.2)	1.6 (1.3)	1.6 (1.3)
— Median (range)	1 (0–4)	1 (0–6)	2 (0–6)
Number of previous AEDs, n (%)			
— ≤2	144 (81.4)	135 (81.3)	91 (80.5)
— >3	33 (18.6)	31 (18.7)	22 (19.5)
Number of concomitant AEDs			
— Mean (SD)	1.9 (0.9)	1.9 (1.1)	2.1 (1.2)
— Median (range)	2 (1–5)	2 (1–10)	2 (1–10)
Number of concomitant AEDs, n (%)			
— 1	67 (37.9)	69 (41.6)	36 (31.9)
— 2	67 (37.9)	59 (35.5)	46 (40.7)
— 3	38 (21.5)	31 (18.7)	24 (21.2)
— ≥4	5 (2.8)	7 (4.2)	7 (6.2)
Daily dose, median (min, max), mg/day[e]			
Up-titration period	741.38 (130.0, 1455.9)	63.79 (18.8, 82.3)	64.59 (18.8, 74.1)
Dose-finding period	1396.43 (964.3, 2810.7)	145.83 (81.3, 340.3)	178.92 (81.3, 340.3)
Maintenance period	1489.68 (776.8, 2997.4)	194.23 (95.2, 399.7)	218.44 (163.6, 399.7)
Treatment period (up-titration, dose-finding, maintenance)	1131.81 (130.0, 2738.4)	131.32 (18.8, 349.5)	165.19 (18.8, 349.5)

AED = antiepileptic drug; FAS = full analysis set; LEV = levetiracetam; Q = quartile; SD = standard deviation; TPM = topiramate.
[a] Patients in the TPM sensitivity subgroup are those who were prescribed TPM within the recommended dose range during the maintenance period. Since all patients in the LEV group received dosages within the recommended range, values for the overall patient group and sensitivity subgroup are identical, and separate values are not provided.
[b] Baseline seizure types are reported according to the International League Against Epilepsy 1981 classification.
[c] In accordance with trial exclusion criteria, no patient had experienced status epilepticus in the 3 months before the start of the baseline period.
[d] Based on data from the full analysis set: LEV n = 176; TPM n = 166; TPM sensitivity subgroup n = 113.
[e] Minimum and maximum doses are based on actual daily doses and may represent a single patient with a single dose deviation on a single day.

analysis was conducted since the mean TPM daily dose during the dose-finding and maintenance periods was <200 mg/day in 70.5% of patients. While the dose cutoffs that defined these subgroups (1500 mg/day for LEV and 200 mg/day for TPM) are representative of clinical practice in Korea [9,11], the results of this posthoc analysis should be interpreted with caution, as the LEV low-dose subgroup is largely in-label, whereas the TPM low-dose subgroup represents an exclusively off-label dosage.

Retention rate is considered to reflect the combined influences of drug efficacy and tolerability on the willingness of patients to continue treatment [10]. However, higher retention rates do not directly indicate greater efficacy or tolerability; they are also affected by numerous factors, such as those related to the patient, disease, and treatment, as well as study design [15]. Therefore, standard efficacy and tolerability measures were also included in this trial. In the FAS, patients who received LEV experienced a numerically greater reduction in seizure frequency, and had a numerically greater ≥50% response rate compared with those who received TPM. Differences in these efficacy outcomes were even greater between the LEV and TPM subgroups in the sensitivity analysis. Of note, a substantially greater proportion of LEV-treated patients experienced 6-month seizure freedom than TPM-treated

Table 2
Primary outcome — retention rate at 52 weeks (full analysis set).
Patients in the sensitivity subgroups are those who were prescribed trial drugs within the recommended dose range during the maintenance period. Since all patients in the levetiracetam group fulfilled this criterion, values for the overall patient group and sensitivity subgroup are identical.

	Overall		Sensitivity subgroups	
	LEV (N = 176)	TPM (N = 166)	LEV (N = 176)	TPM (n = 113)
Patients retained, n (%)	104 (59.1)	94 (56.6)	104 (59.1)	48 (42.5)
Odds ratio[a] for LEV vs TPM (95% CI)	1.1 (0.7, 1.7)		1.9 (1.2, 3.1)	
p value[b]	0.7007		0.0086	

CI = confidence interval; LEV = levetiracetam; TPM = topiramate.
[a] Logistic regression modeling of 52-week retention rate by treatment group and center pooling category.
[b] Calculated from the likelihood ratio test of the treatment group regression coefficient against 0.

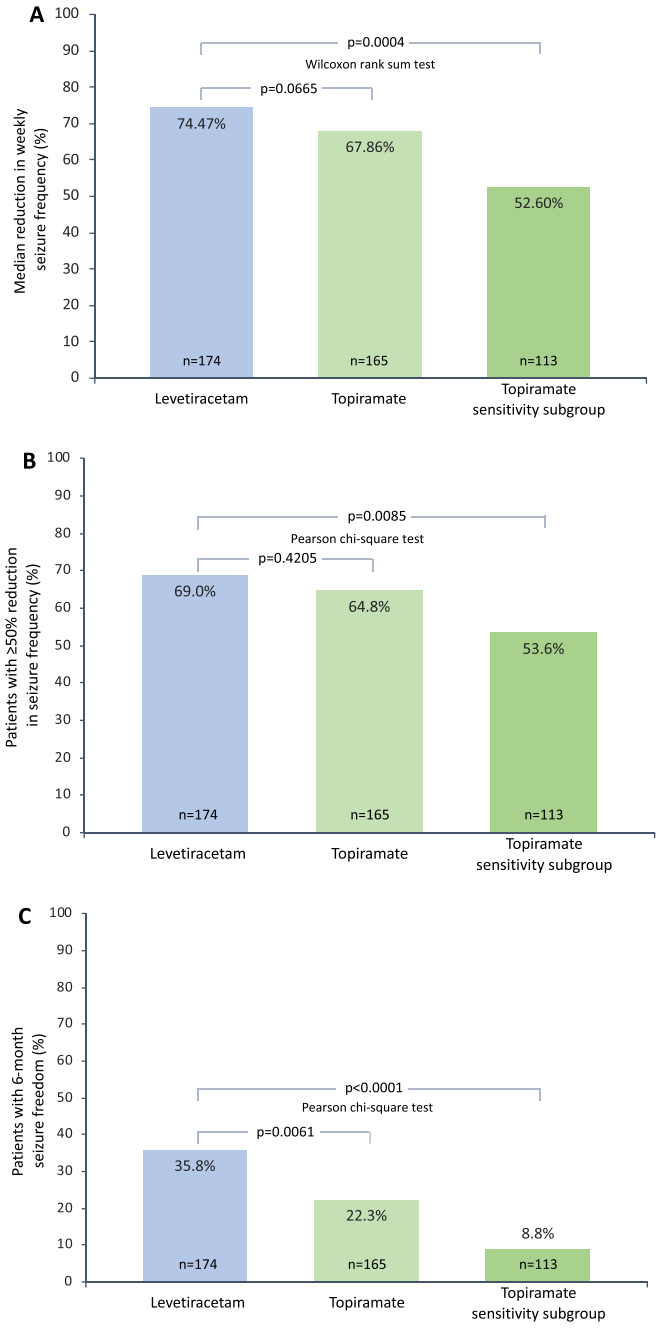

Fig. 3. Efficacy outcomes. Median percent reduction from baseline in weekly focal seizure frequency (A), ≥50% responder rate (B), and 6-month seizure freedom rate during the treatment period (C; full analysis set). p-Values are exploratory.

Table 3
Summary of treatment-emergent adverse events and other safety outcomes (safety set).

	LEV (N = 177)	TPM (N = 166)	TPM sensitivity subgroup[a] (n = 113)
Overview of safety outcomes, n (%)			
Any TEAE	125 (70.6)	128 (77.1)	86 (76.1)
Serious TEAEs	10 (5.6)	15 (9.0)	13 (11.5)
Discontinuations due to TEAEs	14 (7.9)	21 (12.7)	21 (18.6)
TEAEs requiring dose change	12 (6.8)	14 (8.4)	9 (8.0)
Adverse drug reactions[b]	63 (35.6)	76 (45.8)	51 (45.1)
Severe TEAEs	7 (4.0)	6 (3.6)	6 (5.3)
Deaths	0	0	0
TEAEs occurring in ≥5% of patients in any treatment group[c] n (%)			
Somnolence	36 (20.3)	20 (12.0)	15 (13.3)
Dizziness	32 (18.1)	24 (14.5)	16 (14.2)
Nasopharyngitis	24 (13.6)	16 (9.6)	13 (11.5)
Headache	18 (10.2)	24 (14.5)	16 (14.2)
Dyspepsia	9 (5.1)	7 (4.2)	4 (3.5)
Nausea	9 (5.1)	10 (6.0)	6 (5.3)
Tremor	9 (5.1)	0	0
Decreased appetite	3 (1.7)	26 (15.7)	17 (15.0)
Weight decreased	3 (1.7)	17 (10.2)	12 (10.6)
Paresthesia	2 (1.1)	16 (9.6)	10 (8.8)
Aphasia	1 (0.6)	6 (3.6)	6 (5.3)
Memory impairment	1 (0.6)	9 (5.4)	5 (4.4)

LEV = levetiracetam; TEAE = treatment-emergent adverse event; TPM = topiramate.
[a] Patients in the TPM sensitivity subgroup are those who were prescribed TPM within the recommended dose range during the maintenance period. Since all patients in the LEV group fulfilled this criterion, values for the overall patient group and sensitivity subgroup are identical, and separate values are not provided.
[b] Relationship to study drug 'related' or 'missing'
[c] Arranged by most common TEAEs in the LEV safety set group in descending order.

patients, whether in the FAS or in the sensitivity subgroup. We also observed differences in the adverse event (AE) profile between the LEV and TPM groups. Fewer LEV-treated patients reported TEAEs, or discontinued because of TEAEs compared with TPM-treated patients, whether in the primary, sensitivity, or posthoc analyses, with the exception of TEAEs leading to discontinuation in the high-dose subgroups (LEV 1.6% vs TPM 0%). Therefore, LEV appeared to be better tolerated than TPM, even at lower doses. The trend for better tolerability could explain why more patients in the LEV group received in-label doses than patients in the TPM group. Furthermore, the protocol allowed for treatment with lower TPM doses. It is possible that some patients who did not achieve seizure control in the TPM group were not able to receive higher doses due to the aforementioned poorer tolerability of TPM in the Korean population, and remained on a lower-than-recommended dosage. Overall, observations from these efficacy and safety analyses suggest that the use of lower TPM dosages (<200 mg/day) resulted in increased retention in the FAS, but without conferring any marked efficacy, or indeed tolerability advantage over LEV.

In the posthoc analysis, the incidence of TEAEs was lower, and efficacy outcomes were markedly better in the low-dose than in the high-dose groups for both the LEV and TPM treatment arms. A likely explanation is inclusion of patients with less severe epilepsy experiencing seizures that are more easily controlled compared with patients with more severe epilepsy, coupled with the generally greater tolerability of lower AED doses than higher doses.

The effectiveness of LEV and TPM in a Korean population has been compared in another recent study [9]. Differences in design (retrospective, single-center vs prospective, multicenter) and patient population preclude comparison of the results of the study and this trial. However, it is interesting to note that the pattern was similar, in that while the 3-year retention rate was similar for patients with focal seizures treated with LEV or TPM (80.4% vs 79.8%), LEV was found to be significantly better tolerated than TPM ($p < 0.001$); incidence of AEs was 34.4% vs 52.5% and discontinuations due to AEs 6.4% vs 11.1%; TPM was also administered at lower than recommended doses; mean starting dose was 59.2 mg/day and did not exceed 180 mg/day throughout the 3-year study. The investigators attributed the higher level of TPM retention in their study (than that reported elsewhere) to a gradual titration scheme, as well as relatively low maintenance doses. In other comparative studies, retention with LEV has been similar to, or higher than, TPM in diverse populations [5–8], including patients with learning disabilities and elderly patients [16–18]. In these studies, with a single exception, fewer LEV-treated patients discontinued because of TEAEs than TPM-treated patients. In the study that included institutionalized patients with intellectual disability, discontinuation rate was 42% with LEV and 33% with TPM [16].

As noted, this was a prospective, randomized trial; however, its open-label design is its main limitation given the potential for introduction of bias. In Korea, there is greater experience with TPM than with LEV. The former has been available since 1998 and is the third most frequently prescribed AED, after valproate and carbamazepine, based on an analysis of national health insurance data published in 2012 [19]. A similar pediatric analysis, based on prescriptions 2001–2012, also revealed TPM to be one of the most frequently prescribed AEDs [20]. The investigators attributed the low use of LEV to its late introduction in Korea (2007), in addition to its restricted indication in the pediatric population. Consequently, given physicians' greater experience with the use of TPM, the knowledge of which treatment their patients received may have influenced decision-making and patients' response to treatment.

While the primary objective of the trial was not met, LEV was highly effective, with a substantial proportion of patients experiencing 6 months of seizure freedom; LEV's favorable tolerability profile, as confirmed in this trial, also means that patients with more severe disease could potentially benefit from higher doses. Behavioral or psychiatric AEs were reported infrequently in this trial (<5%). Notably, irritability and insomnia were reported in 2.8% (each) of LEV-treated patients, and in 1.8% and 4.2% of TPM-treated patients, respectively, while anxiety and depression were each reported in 1.7% of LEV- and 2.4% of TPM-treated patients. Therapeutic dose ranges can also be achieved fairly rapidly with LEV, and a slow up-titration schedule is not required — patients can receive a clinically effective dose of 1000 mg on the first day of treatment, with titration to the maximum recommended dose of 3000 mg/day occurring over a period of 2–4 weeks [13]. Furthermore, dose adjustment based on concomitant use of enzyme-inducing drugs is not required. In contrast, TPM requires slow titration to reduce the incidence and severity of TEAEs. It should be initiated at 25–50 mg/day followed by titration to an effective dose in 25–50 mg/day increments every week; however, if titration is in increments of 25 mg/day, the time to reach an effective dose can be delayed [12,14]. In effect, up to 16 weeks may be required to attain 400 mg/day. In the second trial conducted by the Korean Topiramate Study Group, conducted specifically to reevaluate dosing and titration schedule, the starting dosage was 25 mg/day followed by weekly 25 mg/day increments until 100 mg/day was reached, then weekly 50 mg/day increments until the target dose of 300 mg/day was attained (8 weeks) [4]. In an open-label prospective study, conducted specifically to evaluate seizure outcomes during the first 15 days of adjunctive LEV and TPM therapy, 26 patients (42.6%) receiving LEV were seizure-free compared with 10 (16.4%) receiving TPM during the initial 15-day treatment period [21]; LEV was initiated at a dose of 250 mg bid, and TPM at a single dose of 50 mg for patients taking a concomitant enzyme-inducing drug and 25 mg for all others.

5. Conclusion

Levetiracetam was not superior to TPM based on the 52-week retention rate for the FAS. However, a large proportion of patients in the TPM group took doses that were lower than the recommended range, which could have led to a higher-than-expected retention rate in these patients, due to the greater tolerability of lower TPM doses. In the sensitivity analysis, which included only data from patients who were prescribed drug doses in the recommended range during the maintenance period, retention was considerably higher among LEV-treated patients (same as the FAS) than TPM-treated patients. The open-label design of the trial may have influenced the results, given the greater experience with the use of TPM in Korea. Treatment with LEV was associated with clinically impactful efficacy, as demonstrated by the high seizure-freedom rate, as well as a more favorable safety and tolerability profile compared with TPM. Consequently, with its straightforward dosing and titration schedule, many patients with focal seizures in Korea could benefit from treatment with LEV.

Funding

This trial was sponsored by UCB Pharma. The sponsor was responsible for designing and conducting the trial, as well as collection, analysis, and interpretation of data.

Declaration of Competing Interest

Sang Kun Lee, Sang Ahm Lee, Dong Wook Kim, and Byungin Lee have no conflicts of interest. Christian Loesch and Toru Osakabe are employees of UCB Pharma. Barbara Pelgrims is an employee of and receives stock options from UCB Pharma.

Acknowledgments

The authors wish to thank the patients who participated in the trial and their caregivers, as well as the investigators and their teams who contributed to the trial.

The authors also thank Kyoko Hirano (UCB Pharma, Tokyo, Japan) for critical review and coordination of manuscript preparation, HyeongDu Lee (UCB Pharma, Seoul, Republic of Korea) for facilitating manuscript development, and JiEun Lee (formerly UCB Pharma, Republic of Korea) for her contribution to the study.

Medical writing support was provided by Jessica Gamage, PhD, QXV Communications (an Ashfield Business, part of UDG Healthcare plc, Macclesfield, UK), and Azita Tofighy, funded by UCB Pharma.

N01353 trial group

Yong-Won Cho, MD, Keimyung University Dongsan Hospital; Sung-Pa Park, MD, Kyungpook National University Hospital, Daegu; Kyoung Heo, MD, ByungIn Lee, MD, Severance Hospital, Yonsei University Health System; Bong Seung Hong, MD, Samsung Medical Center; Dong-Wook Kim, MD, KonKuk University Hospital; Ji Hyun Kim, MD, Korea University Guro Hospital; Sang Kun Lee, MD, Seoul National University Hospital; Hong-Ki Song, MD, Gangdong Sacred Heart Hospital; Young Min Shon, MD, The Catholic University of Korea, St. Mary's Hospital, and Yeouido St. Mary's Hospital; Young In Kim, MD, The Catholic University of Korea, St. Mary's Hospital; Woo jun Kim, MD, The Catholic University of Korea, Yeouido St. Mary's Hospital; Bo Mi Kim, MD, Sang Ahm Lee, MD, Asan Medical Center, Seoul; Sang-Hyun Jang, MD, Eulji University Hospital; Jae Moon Kim, MD, Chungnam National University Hospital, Daejeon; KiHwan Ji, MD, Inje University Busan Paik Hospital Medical Center; Sang-Ho Kim, MD, Dong A University Medical Center; Sung Eun Kim, MD, Inje University Haeundae Paik Hospital; Je Yong Son, MD, Bongseng Memorial Hospital; Soon Kee No, MD, Bongseng Memorial Hospital, Busan; Kwang-Ki Kim, MD, Dongguk University International Hospital; Pamela Song, MD, Inje University Ilsan Paik Hospital; Hee Kyung Park, MD, Inje University Ilsan Paik Hospital, Goyang-si; Myeong Kyu Kim, MD, Chonnam National University Hospital, Gwangju; Joo-Yong Kim, MD, Hallym University Medical Center, Anyang; OkJoon Kim, MD, Bundang CHA Medical Center, Seongnam-si; Eun Mi Lee, MD, Ulsan University Hospital, Ulsan; Sung-Chul Lim, MD, The Catholic University of Korea, St. Vincent's Hospital, Suwon-si; Dong-Jin Shin, MD, Gachon University Gil Hospital, Incheon.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.05.014.

References

[1] Heo K, Lee BI, Yi SD, Huh K, Kim JM, Lee SA, et al. Efficacy and safety of levetiracetam as adjunctive treatment of refractory partial seizures in a multicentre open-label single-arm trial in Korean patients. Seizure 2007;16:402–9.

[2] Kang BS, Moon HJ, Kim YS, Lee ST, Jung KH, Chu K, et al. The long-term efficacy and safety of levetiracetam in a tertiary epilepsy entre. Epileptic Disord 2013;15:302–10.
[3] Korean Topiramate Study Group. Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial. Korean Topiramate Study Group. Epilepsia 1999;40:1767–74.
[4] Korean Topiramate Study Group. Low dose and slow titration of topiramate as adjunctive therapy in refractory partial epilepsies: a multicentre open clinical trial. Seizure 2002;11:255–60.
[5] Bootsma HP, Ricker L, Diepman L, Gehring J, Hulsman J, Lambrechts D, et al. Long-term effects of levetiracetam and topiramate in clinical practice: a head-to-head comparison. Seizure 2008;17:19–26.
[6] Chung S, Wang N, Hank N. Comparative retention rates and long-term tolerability of new antiepileptic drugs. Seizure 2007;16:296–304.
[7] Peltola J, Peltola M, Auvinen A, Raitanen J, Fallah M, Keränen T. Retention rates of new antiepileptic drugs in localization-related epilepsy: a single-center study. Acta Neurol Scand 2009;119:55–60.
[8] Mäkinen J, Peltola J, Raitanen J, Alapirtti T, Rainesalo S. Comparative effectiveness of eight antiepileptic drugs in adults with focal refractory epilepsy: the influence of age, gender, and the sequence in which drugs were introduced onto the market. J Neurol 2017;264:1345–53.
[9] Sunwoo JS, Park BS, Ahn SJ, Hwang S, Park CY, Jun JS, et al. Three-year retention rates of levetiracetam, topiramate, and oxcarbazepine: a retrospective hospital-based study. Clin Neuropharmacol 2017;40:56–62.
[10] Ben-Menachem E, Sander JW, Privitera M, Gilliam F. Measuring outcomes of treatment with antiepileptic drugs in clinical trials. Epilepsy Behav 2010;18:24–30.
[11] Cho YJ, Heo K, Kim WJ, Jang SH, Jung YH, Ye BS, et al. Long-term efficacy and tolerability of topiramate as add-on therapy in refractory partial epilepsy: an observational study. Epilepsia 2009;50:1910–9.
[12] US Food and Drug Administration. Topiramate prescribing information. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020844s041lbl.pdf; 2012, Accessed date: May 2019.
[13] US Food and Drug Administration. Levetiracetam prescribing information. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021035s099,021505s038lbl.pdf; 2017, Accessed date: May 2019.
[14] European Medicines Agency. Topiramate prescribing information. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Topamax_30/WC500018620.pdf; 2009, Accessed date: May 2019.
[15] Lhatoo SD, Wong IC, Sander JW. Prognostic factors affecting long-term retention of topiramate in patients with chronic epilepsy. Epilepsia 2000;41:338–41.
[16] Carpay JA, Aalbers K, Graveland GA, Engelsman M. Retention of new AEDs in institutionalized intellectually disabled patients with epilepsy. Seizure 2009;8:119–23.
[17] Simister RJ, Sander JW, Koepp MJ. Long-term retention rates of new antiepileptic drugs in adults with chronic epilepsy and learning disability. Epilepsy Behav 2007;10:336–9.
[18] Arif H, Buchsbaum R, Pierro J, Whalen M, Sims J, Resor Jr SR, et al. Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. Arch Neurol 2010;67:408–15.
[19] Lee SY, Jung KY, Lee IK, Do Yi Sang, Cho Yong Won, Kim Dong Wook, et al. Prevalence of treated epilepsy in Korea based on national health insurance data. J Korean Med Sci 2012;27:285–90.
[20] Cho YS, Ah YM, Jung AH, Kim KJ, Lee JY. Trends in antiepileptic drug prescriptions for childhood epilepsy at a tertiary children's hospital in Korea. Paediatr Drugs 2001-2012;17:487–96 2015.
[21] Specchio LM, Boero G, Specchio N, De Agazio G, De Palo A, de Tommaso M, et al. Evidence for a rapid action of levetiracetam compared to topiramate in refractory partial epilepsy. Seizure 2006;15:112–6.