



Adjunctive levetiracetam in the treatment of Chinese and Japanese adults with generalized tonic–clonic seizures: A double-blind, randomized, placebo-controlled trial

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SUMMARY

Objective: To assess the efficacy, safety, and tolerability of adjunctive levetiracetam (LEV) in Chinese and Japanese adults with generalized tonic–clonic (GTC) seizures (N01159; NCT01228747).

Methods: This double-blind, randomized, placebo-controlled, multicenter phase III trial comprised: 4-week retrospective and 4-week prospective baseline, 12-week dose-adjustment, and 16-week evaluation periods. Chinese and Japanese patients ≥ 16 years old with idiopathic generalized, symptomatic generalized, or undetermined epilepsy with GTC seizures received a single-blind placebo during the prospective baseline, and then were randomized 1:1 to placebo or LEV 1,000 mg/day administered twice daily. Patients reporting GTC seizures up to week 8 had the LEV dosage increased to 3,000 mg/day. The primary efficacy variable was percent reduction from combined baseline in GTC seizures/week during the 28-week treatment period.

Results: Overall, 251 patients were randomized (208 from China; 43 from Japan); 141 (56.2%) completed the 28-week treatment period. Least-squares mean percent reduction from combined baseline in GTC seizures/week (treatment period) was placebo 12.6% versus LEV 68.8% (95% confidence interval, 44.0–68.2; $p < 0.0001$). GTC seizure frequency reduction occurred in both patients with idiopathic and symptomatic generalized epilepsy. The 50% responder rate (treatment period) was placebo 28.4% versus LEV 77.8%. Freedom from GTC seizures (evaluation period) was placebo 3.1% versus LEV 29.6%. Incidence of treatment-emergent adverse events (TEAEs; treatment period) was placebo 52.0% versus LEV 57.1%; most frequently nasopharyngitis, protein in urine, decreased platelet count, and pyrexia. Incidence of TEAEs leading to discontinuation was 4.8% versus 3.2%; incidence of serious TEAEs was 3.2% versus 0.8% for placebo and LEV, respectively; 3 patients taking placebo died versus none taking LEV.

Significance: In this trial, adjunctive LEV 1,000–3,000 mg/day was effective in reducing GTC seizure frequency in Chinese and Japanese patients ≥ 16 years old with GTC seizures. Seizure reduction occurred in both patients with idiopathic and symptomatic generalized epilepsy. LEV was well tolerated in this population.

KEY WORDS: Levetiracetam, Generalized tonic–clonic seizure, Safety/tolerability, Efficacy.

Generalized tonic–clonic (GTC) seizures are the most common generalized seizure type.^{1,2} GTC seizures may occur in patients with idiopathic generalized epilepsy, symptomatic generalized epilepsy, or cryptogenic generalized epilepsy, as well as in those with undetermined epilepsy. The convulsive nature of GTC seizures means that

they can result in injury and are a risk factor for seizure-related comorbidities and complications.¹ The International League Against Epilepsy (ILAE) evidence-based treatment guidelines have reported evidence of efficacy or effectiveness in double-blind or open-label randomized, controlled trials in adults with GTC seizures for several antiepileptic

KEY POINTS

- LEV was assessed in Chinese and Japanese patients with GTC seizures uncontrolled by 1–2 antiepileptic drugs (AEDs) for 28 weeks
- This double-blind trial randomized 251 patients (208 from China; 43 from Japan)
- Reduction in GTC seizures was seen for the primary efficacy variable ($p < 0.0001$)
- GTC seizure reduction occurred in both patients with idiopathic and symptomatic generalized epilepsy
- Adjunctive LEV was well tolerated in this population

drugs (AEDs), including carbamazepine, lamotrigine, levetiracetam (LEV), phenytoin, topiramate, and valproate.³ Since the guidelines were published, efficacy in primary GTC seizures has also been reported for perampanel.⁴

Levetiracetam is a well-established second-generation AED. It is effective as adjunctive treatment for focal (partial-onset) seizures in adults,^{5–7} children,⁸ and infants,⁹ and as monotherapy in adults with focal seizures.¹⁰ Adjunctive LEV was found to be efficacious in the treatment of patients with myoclonic seizures associated with idiopathic generalized epilepsy.¹¹ In a double-blind, randomized, placebo-controlled trial (N01057/NCT00160550) of patients aged 4–65 years with GTC seizures associated with idiopathic generalized epilepsy uncontrolled by 1–2 AEDs, there was a statistically significant improvement in both primary and secondary efficacy outcomes in patients treated with LEV compared with placebo. Adjunctive LEV was also generally well tolerated in this population, with few discontinuations.¹² A supplementary analysis of data from these 2 trials in idiopathic generalized epilepsy^{11,12} showed that adjunctive LEV provided effective seizure control in patients with juvenile absence epilepsy, juvenile myoclonic epilepsy, and GTC seizures on awakening.¹³ Efficacy for GTC seizures was sustained for a median of 2.1 years in the open-label, long-term, follow-up trial and treatment-emergent adverse events (TEAEs) did not appear to increase in incidence over time.¹⁴

Results from subsequent clinical trials have supported the use of LEV in Chinese¹⁵ and Japanese patients^{16–18} with focal epilepsy. Several formulations of LEV have been

approved in Japan (tablets, dry syrup, and injection) and in China (tablets, syrup, and injection) for adjunctive treatment of focal seizures in children aged ≥ 4 years and in adults; more recently, the oral LEV solution has also been approved in China for use in children aged ≥ 1 years. The current report describes the first collaborative trial for LEV between China and Japan, conducted to assess efficacy, safety, and tolerability of adjunctive LEV among Chinese and Japanese adults with GTC seizures. Unlike the former study (N01057),¹² the inclusion criteria were expanded to allow inclusion of not only patients with idiopathic generalized epilepsy with GTC seizures, but also patients with symptomatic, cryptogenic, or undetermined epilepsy with GTC seizures, to increase recruitment. There had been some evidence that LEV might prove to be effective in treating GTC seizures in patients with symptomatic generalized epilepsy.^{19–23}

METHODS

Trial design

This was a double-blind, randomized, parallel-group, placebo-controlled, multicenter phase III trial, conducted between October 2010 and May 2014 at 20 sites in China and 95 sites in Japan (N01159; NCT01228747). An 8-week combined baseline period comprised a 4-week retrospective baseline period and a 4-week prospective baseline period, except for patients without documented historical seizure information, who had to complete an 8-week prospective baseline period (Fig. S1). During the prospective baseline period, all patients received single-blind placebo oral tablets twice daily.

Patients were randomized 1:1 to placebo or LEV using central randomization via an interactive voice response system (IVRS), stratified by country (China, Japan) and baseline seizure frequency (≥ 1 or < 1 seizure/week). After randomization, a 12-week dose-adjustment period was followed by a 16-week evaluation period (overall 28-week treatment period). Patients assigned to LEV started treatment on 1,000 mg/day, in 2 divided doses, and seizure frequency was assessed at weeks 4 and 8. Patients who had no GTC seizures up to week 8 after randomization were maintained at LEV 1,000 mg/day, whereas for those who had ≥ 1 GTC

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seizure, LEV was increased to 3,000 mg/day in steps of 1,000 mg/day/2 weeks. During the first 2 weeks on 3,000 mg/day, patients were allowed to reduce LEV to 2,000 mg/day for tolerability reasons at the investigator's discretion. The dose then remained stable during the evaluation period. At the end of the evaluation period, patients either entered a 6-week withdrawal period with a final safety visit 2 weeks after the last dose (LEV was reduced in steps of 1,000 mg/day/2 weeks), or entered a 4-week transition period to open-label LEV. After transition, patients in China could continue with LEV treatment by enrolling in a named patient program, whereas those in Japan could enter an open-label extension trial (N01361; NCT01398956). Patients who discontinued due to lack of efficacy after receiving a stable dose of study drug for ≥ 8 weeks also had the option to transition to the named patient program or open-label extension trial.

Patients

Chinese and Japanese patients ≥ 16 years old with uncontrolled GTC seizures (based on the ILAE Classification of epileptic seizures)²⁴ despite treatment with 1 or 2 AEDs could take part in the trial. Patients with idiopathic generalized epilepsy, symptomatic generalized epilepsy, cryptogenic generalized epilepsy, or undetermined epilepsy with GTC seizures were included. Patients had to have ≥ 3 GTC seizures during the combined baseline period, with ≥ 1 GTC seizure occurring during both the retrospective and prospective baseline periods. Electroencephalography (EEG) conducted within 1 year before the prospective baseline period was required. Generalized and diffuse EEG features were treated as eligible unless they indicated Lennox-Gastaut syndrome, focal seizures, or focal epilepsy. Dosing of 1–2 AEDs was required to be stable for 4 weeks (12 weeks for potassium bromide and sodium bromide) before the baseline period and during the trial. Key exclusion criteria were diagnosis of focal epilepsy confirmed by EEG and magnetic resonance imaging (MRI); signs suggesting a progressive brain lesion or disorder confirmed by computed tomography (CT) or MRI; history of status epilepticus within 3 months prior to trial enrollment; and previous treatment with LEV. Patients with psychogenic nonepileptic seizures or clinically significant acute or chronic illness were also excluded. Patients with Lennox-Gastaut syndrome were excluded because evidence from a very small trial suggested that LEV may not be efficacious for tonic seizures.²⁵

This trial was conducted in accordance with the International Conference on Harmonization – Good Clinical Practice requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved. Patients or their

parents/legal representatives gave their written informed consent before procedures began.

Assessments

Patients recorded date, time, frequency and symptoms of seizures, adverse events, and concomitant therapies/medications on a daily record card. These were reviewed by the investigator at each trial visit.

Safety and tolerability assessments included TEAEs classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0, laboratory assessments, electrocardiogram (ECG), vital signs, and body weight.

Blood samples were taken every 4 weeks during weeks 4–32 for analysis of LEV plasma concentrations.

Statistical analysis

Sample size was based on results of a pivotal double-blind, randomized, placebo-controlled trial (N01057)¹² of patients with GTC seizures. A sample size of 116 patients per treatment group was required to detect a treatment difference of 26.6% between placebo and LEV for mean percent change from baseline in GTC seizures/week (assuming a common standard deviation [SD] of 62.2%), with 90% power, at a 2-sided significance level of 0.05. This calculation assumed that a 10% dilution of treatment effect might occur, as the current trial allowed doses of LEV 1,000 mg/day as well as LEV 3,000 mg/day, compared with the aforementioned trial, which included LEV 3,000 mg/day only.

The safety population comprised all patients who received ≥ 1 dose of trial drug after randomization. The full analysis set comprised all patients in the safety population with ≥ 1 GTC seizure during the combined baseline period (i.e., an evaluable baseline) and ≥ 1 post-baseline GTC seizure count data point. The per-protocol set was a subset of the full analysis set and included patients without important protocol deviations affecting the primary efficacy variable; protocol-compliant data collected from patients prior to a protocol deviation were included in the per-protocol set, confirmed prior to trial unblinding. The pharmacokinetic (PK) per-protocol set was a subset of the safety population and included patients randomized to receive LEV, with ≥ 1 PK measurement and no important protocol deviations affecting the PK measurement.

The primary efficacy variable was percent reduction from combined baseline in GTC seizures/week during the treatment period. The primary efficacy analysis was based on an analysis of covariance (ANCOVA) on the variable using treatment (LEV and placebo) and country (China and Japan) as factors, and GTC seizures/week during the combined baseline period as a continuous covariate. Statistical significance was based on $\alpha = 0.05$. The primary efficacy variable was also analyzed by country and by epilepsy type.

Secondary efficacy variables included percent reduction from combined baseline in GTC seizures/week during the 16-week evaluation period, 50% responder rate (defined as

percentage of patients with $\geq 50\%$ reduction from combined baseline in GTC seizures/week) during the treatment and evaluation periods, freedom from GTC seizures during the evaluation period, and freedom from all seizure types during the evaluation period. Statistical tests for these efficacy variables were exploratory only. A nonparametric sensitivity analysis (van Elteren test) of the full analysis set was conducted to confirm the primary (parametric) analysis. Percent reduction in GTC seizures/week from combined baseline during the evaluation period was assessed by ANCOVA, as for the primary efficacy variable. The 50% responder rates were based on a logistic regression model with predictors of treatment, country, and combined baseline GTC seizures/week (as a continuous variable); estimated odds ratios and 95% confidence intervals (CIs) were also calculated. LEV plasma concentrations were analyzed using descriptive statistics, including geometric mean and geometric coefficient of variation.

For patients who discontinued, data from the early discontinuation visit were considered as the next scheduled visit. There was no imputation of missing data.

RESULTS

Patient disposition

In total, 251 patients were randomized: 208 from China and 43 from Japan (Fig. 1). Of these, 25 patients were excluded due to insufficient trial management ($n = 16$), no post-baseline seizure data ($n = 8$), and patient re-diagnosed with focal seizures after randomization ($n = 1$). The remaining 226 patients were included in the full analysis set. Overall, 141 (56.2%) of 251 patients completed the 28-week treatment period, and 208 patients (82.9%) planned to receive LEV in a named patient program (China) or enter the open-label extension study (Japan). Fifty-three patients received LEV 1,000 mg/day, 73 received LEV 2,000–3,000 mg/day, and 125 received placebo during the treatment period (safety population).

Demographics and baseline characteristics

Patient demographic and baseline characteristics were broadly similar in the placebo and LEV groups (Table 1). Patients had a mean age (SD) of 32.2 (11.9) years and 155/251 (61.8%) were male. Mean epilepsy duration was 16.7 years. All patients reported history of GTC seizures (with the exception of 1 Japanese patient randomized to placebo, who was subsequently re-diagnosed with focal epilepsy). History of other generalized seizure types included absence and tonic seizures; low proportions of focal and unclassified seizures were also reported. Most patients did not have a specified epilepsy type recorded; patients with other idiopathic epilepsies (41.0%) and other symptomatic epilepsies (48.2%) were in the majority. Most patients' epilepsy was of unknown etiology (90.4%). Almost all patients (250/251; 99.6%) were taking ≥ 1 concomitant AED; the

most frequently used concomitant AEDs were valproate (37.8%), carbamazepine (31.5%), and lamotrigine (15.9%).

Efficacy

Primary efficacy variable

Least-squares mean (standard error [SE]) percent reduction from combined baseline in GTC seizures/week during the treatment period was 12.6% (4.4%) in the placebo group compared with 68.8% (4.3%) in the LEV group. The difference between groups was statistically significant (95% CI 44.0–68.2; $p < 0.0001$; Fig. 2A). The median (interquartile range [IQR]) percent reduction from combined baseline in GTC seizures/week during the 28-week treatment period was 19.6% (–8.4, 52.8) in the placebo group versus 77.0% (53.6, 99.0) in the LEV group. Results for the primary efficacy variable were similar in Chinese (LEV versus placebo, $p < 0.0001$) and Japanese (LEV vs. placebo, $p = 0.0280$) patients.

Similar results were observed in subgroups of patients with idiopathic generalized epilepsy and symptomatic generalized epilepsy. Median (IQR) percent reduction from combined baseline in GTC seizures/week during the treatment period for placebo versus LEV was 27.0% (–7.2, 57.9) versus 73.9% (54.7, 94.8) in patients with idiopathic generalized epilepsy, and 13.8% (–8.8, 52.6) versus 78.7% (50.9, 100.0) in patients with symptomatic generalized epilepsy (Fig. 2B).

Consistent with the findings in the full analysis set, analysis of the per-protocol set showed that patients treated with LEV had a median percent reduction in GTC seizures/week of 77.0% (95% CI, 69.6–86.2) compared with a reduction of 22.8% (95% CI, 10.2–36.0) among placebo-treated patients. In addition, nonparametric sensitivity analysis (van Elteren test) of the full analysis set confirmed the robustness of the primary (parametric) analysis ($p < 0.0001$ for LEV vs. placebo).

Secondary efficacy variables

Least-squares mean (SE) percent reduction from combined baseline in GTC seizures/week during the evaluation period was 4.2% (11.3%) for the placebo group compared with 68.5% (10.7%) for the LEV group. Median percent reduction in GTC seizures/week is presented in Figure 3A.

The 50% responder rate was higher among LEV-treated patients than placebo-treated patients during both the treatment and evaluation periods (Fig. 3B).

Freedom from GTC seizures during the evaluation period was attained by 3.1% in the placebo group versus 29.6% in the LEV group (Table 2). Freedom from all seizure types during the evaluation period was achieved by 2.1% (95% CI, 0.3–7.3) of patients in the placebo group versus 25.9% (95% CI, 18.0–35.2) of patients in the LEV group.

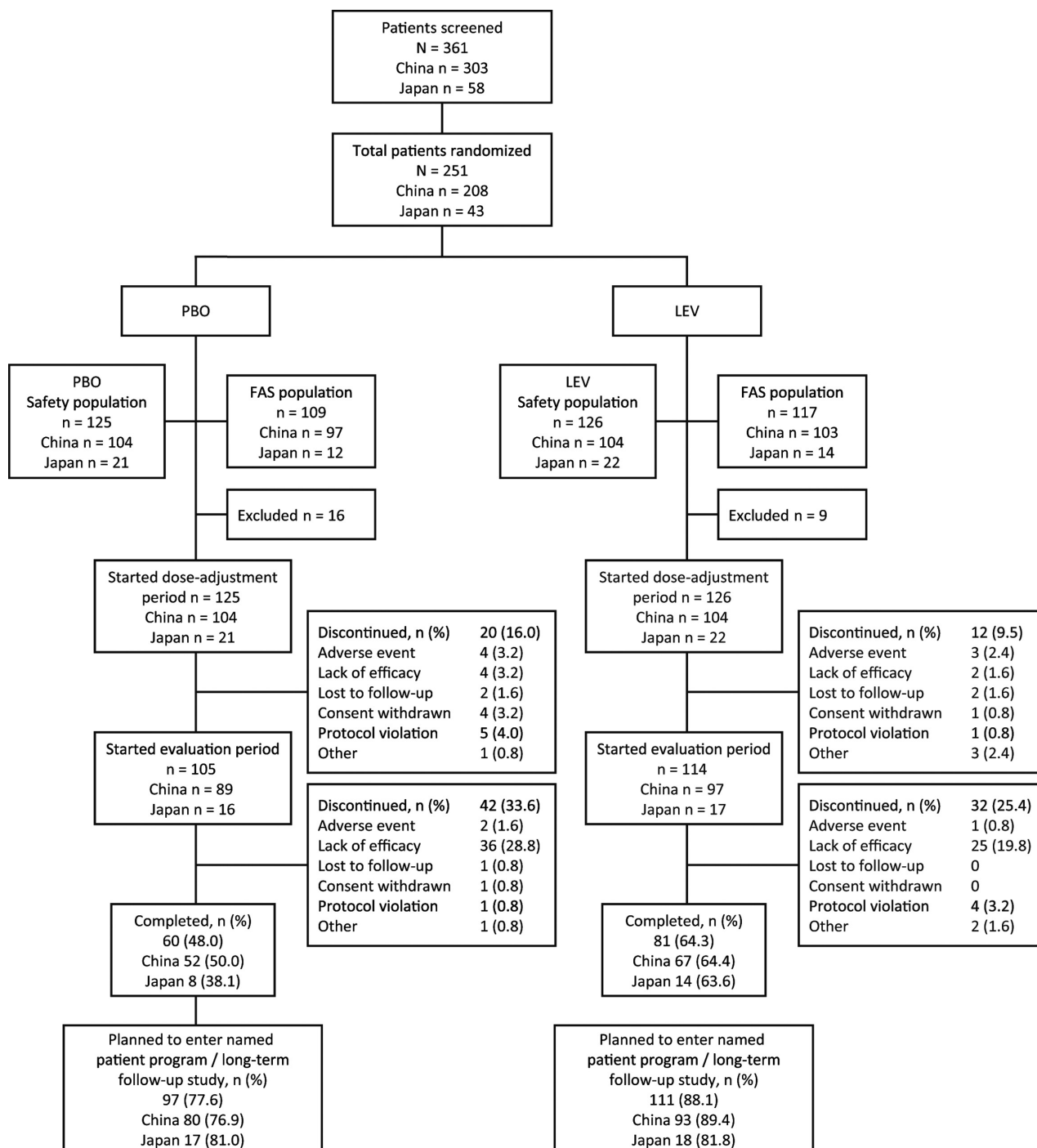


Figure 1. Patient disposition. FAS, full analysis set; LEV, levetiracetam; PBO, placebo. *Epilepsia Open* © ILAE

Safety and tolerability

Patients in the LEV group were exposed to LEV for a median of 84.0 days (range 2.0–98.0) in the dose-adjustment period and 112.0 days (range 35.0–156.0) in the evaluation period. Patients in the overall LEV group and the Chinese and Japanese LEV groups received a mean (SD) LEV dose of

1,594.8 (548.8) mg/day, 1,640.9 (550.2) mg/day, and 1,377.0 (497.4) mg/day during the dose-adjustment period, and 2,207.4 (970.9) mg/day, 2,264.3 (960.9) mg/day, and 1,882.4 (992.6) mg/day during the evaluation period, respectively.

Overall, the incidence of TEAEs during the treatment period was higher in the LEV group (57.1%) than in the placebo

Table 1. Patient demographics and baseline characteristics (safety population)

	Overall		China		Japan	
	Placebo (n = 125)	LEV (n = 126)	Placebo (n = 104)	LEV (n = 104)	Placebo (n = 21)	LEV (n = 22)
Age, mean (SD), years	32.8 (12.5)	31.5 (11.3)	33.0 (13.1)	31.3 (11.0)	32.0 (9.6)	32.7 (13.1)
Gender, male, n (%)	76 (60.8)	79 (62.7)	62 (59.6)	67 (64.4)	14 (66.7)	12 (54.5)
Race, n (%)						
Chinese	104 (83.2)	104 (82.5)	104 (100)	104 (100)	0	0
Japanese	21 (16.8)	22 (17.5)	0	0	21 (100)	22 (100)
Duration of epilepsy, mean (SD), years	16.3 (12.1)	17.0 (11.8)	15.9 (11.6)	16.1 (11.5)	18.5 (14.4)	21.0 (12.4)
Seizure history, n (%)						
Focal	5 (4.0)	6 (4.8)	0	1 (1.0)	5 (23.8)	5 (22.7)
Generalized	124 (99.2)	126 (100.0)	104 (100.0)	104 (100.0)	20 (95.2)	22 (100)
Absence	9 (7.2)	8 (6.3)	8 (7.7)	6 (5.8)	1 (4.8)	2 (9.1)
Atypical absence	4 (3.2)	2 (1.6)	4 (3.8)	1 (1.0)	0	1 (4.5)
Myoclonic	0	3 (2.4)	0	1 (1.0)	0	2 (9.1)
Clonic	2 (1.6)	0	1 (1.0)	0	1 (4.8)	0
Tonic	6 (4.8)	5 (4.0)	1 (1.0)	0	5 (23.8)	5 (22.7)
Tonic-clonic	124 (99.2)	126 (100.0)	104 (100.0)	104 (100.0)	20 (95.2)	22 (100)
Atonic	1 (0.8)	3 (2.4)	1 (1.0)	1 (1.0)	0	2 (9.1)
Unclassified	4 (3.2)	1 (0.8)	0	0	4 (19.0)	1 (4.5)
Cluster seizures	4 (3.2)	2 (1.6)	0	1 (1.0)	4 (19.0)	1 (4.5)
Classification of epilepsy type, n (%)						
Focal	1 (0.8)	0	0	0	1 (4.8)	0
Generalized	120 (96.0)	120 (95.2)	103 (99.0)	103 (99.0)	17 (81.0)	17 (77.3)
Idiopathic ^a	58 (46.4)	59 (46.8)	46 (44.2)	46 (44.2)	12 (57.1)	13 (59.1)
Juvenile myoclonic epilepsy	3 (2.4)	3 (2.4)	0	1 (1.0)	3 (14.3)	2 (9.1)
Epilepsy with grand mal seizures on awakening	6 (4.8)	2 (1.6)	4 (3.8)	2 (1.9)	2 (9.5)	0
Other	49 (39.2)	54 (42.9)	42 (40.4)	43 (41.3)	7 (33.3)	11 (50.0)
Symptomatic ^b	62 (49.6)	61 (48.4)	57 (54.8)	57 (54.8)	5 (23.8)	4 (18.2)
Specific syndromes	2 (1.6)	0	2 (1.9)	0	0	0
Other	60 (48.0)	61 (48.4)	55 (52.9)	57 (54.8)	3 (14.3)	5 (22.7)
Undetermined ^c	4 (3.2)	6 (4.8)	1 (1.0)	1 (1.0)	3 (14.3)	5 (22.7)
Seizure frequency during 8-week baseline, median (range)	7.0 (3–259)	7.5 (3–230)	8.0 (3–109)	8.0 (3–136)	5.0 (3–259)	7.0 (3–230)
Prior AEDs, ≥1, n (%)	70 (56.0)	76 (60.3)	55 (52.9)	59 (56.7)	15 (71.4)	17 (77.3)
Concomitant AEDs, n (%)						
Any	125 (100.0)	125 (99.2)	104 (100.0)	103 (99.0)	21 (100.0)	22 (100.0)
Valproate	50 (40.0)	45 (35.7)	38 (36.5)	29 (27.9)	12 (57.1)	16 (72.7)
Carbamazepine	42 (33.6)	37 (29.4)	33 (31.7)	33 (31.7)	9 (42.9)	4 (18.2)
Lamotrigine	18 (14.4)	22 (17.5)	16 (15.4)	20 (19.2)	2 (9.5)	2 (9.1)
Topiramate	16 (12.8)	20 (15.9)	13 (12.5)	17 (16.3)	3 (14.3)	3 (13.6)
Phenobarbital	18 (14.4)	15 (11.9)	15 (14.4)	12 (11.5)	3 (14.3)	3 (13.6)
Oxcarbazepine	16 (12.8)	12 (9.5)	16 (15.4)	12 (11.5)	0	0

AED, antiepileptic drug; LEV, levetiracetam; SD, standard deviation.

^aNo cases of benign neonatal familial convulsions, benign neonatal convulsions, benign myoclonic epilepsy in infancy, childhood absence epilepsy, or juvenile absence epilepsy were reported.

^bNo cases of early myoclonic encephalopathy or early infantile epileptic encephalopathy with suppression-burst were reported.

^cEpilepsies and syndromes that were undetermined to be focal or generalized.

group (52.0%; Table 3). Most were mild-to-moderate in intensity. Most frequently reported TEAEs were nasopharyngitis (placebo 16.0% vs. LEV 19.0%), presence of protein in urine (0.8% vs. 7.9%), decreased platelet count (3.2% vs. 5.6%), and pyrexia (4.0% vs. 5.6%), respectively. Incidence of TEAEs in Chinese patients was similar to that of the overall safety population. Incidence of TEAEs was higher among Japanese patients, both in placebo (15/21; 71.4%) and LEV (20/22; 90.9%) groups. Incidence of individual TEAEs reported was broadly similar to the overall safety population, although Japanese patient numbers were

too small to draw any conclusions. A total of 5 patients (4.0%) in the placebo group and 6 patients (4.8%) in the LEV group reported psychiatric TEAEs. Psychiatric TEAEs reported in the placebo group were insomnia (2/125; 1.6%), anxiety (1/125; 0.8%), hypomania (1/125; 0.8%), and social phobia (1/125; 0.8%); in the LEV group they were insomnia (2/126; 1.6%), irritability (2/126; 1.6%), psychotic disorder (1/126; 0.8%), and suicidal ideation (1/126; 0.8%).

The most commonly reported drug-related TEAEs as assessed by the investigator were presence of protein in urine (0.8% placebo vs. 7.1% LEV), decreased platelet

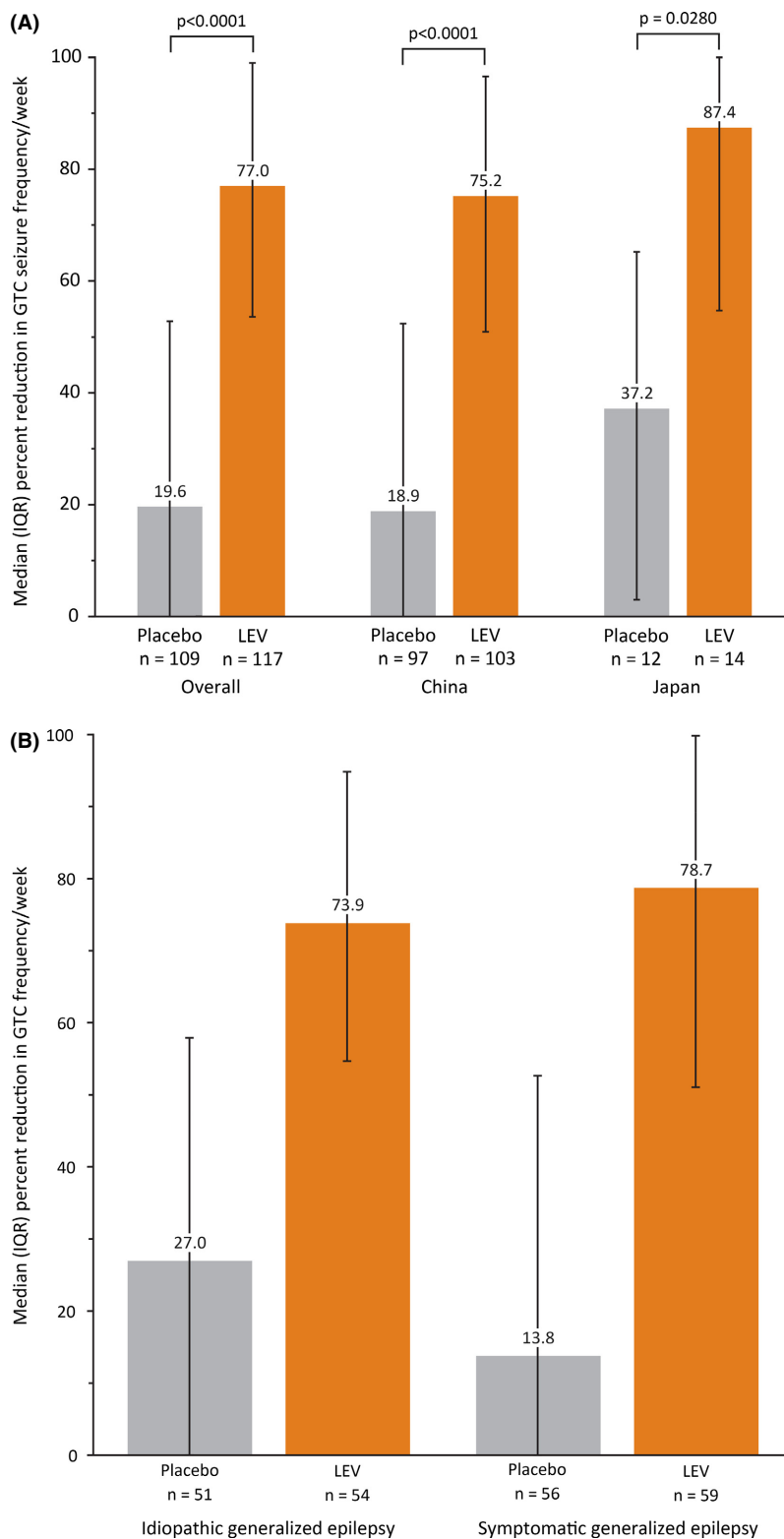


Figure 2.

A, Median percent reduction from combined baseline in generalized tonic–clonic seizures/week during the 28-week treatment period (full analysis set); p-values versus placebo calculated using ANCOVA. **B**, Median percent reduction from combined baseline in generalized tonic–clonic seizures/week for patients with idiopathic and symptomatic generalized epilepsy during the 28-week treatment period. ANCOVA, analysis of covariance; GTC, generalized tonic–clonic; IQR, interquartile range; LEV, levetiracetam.

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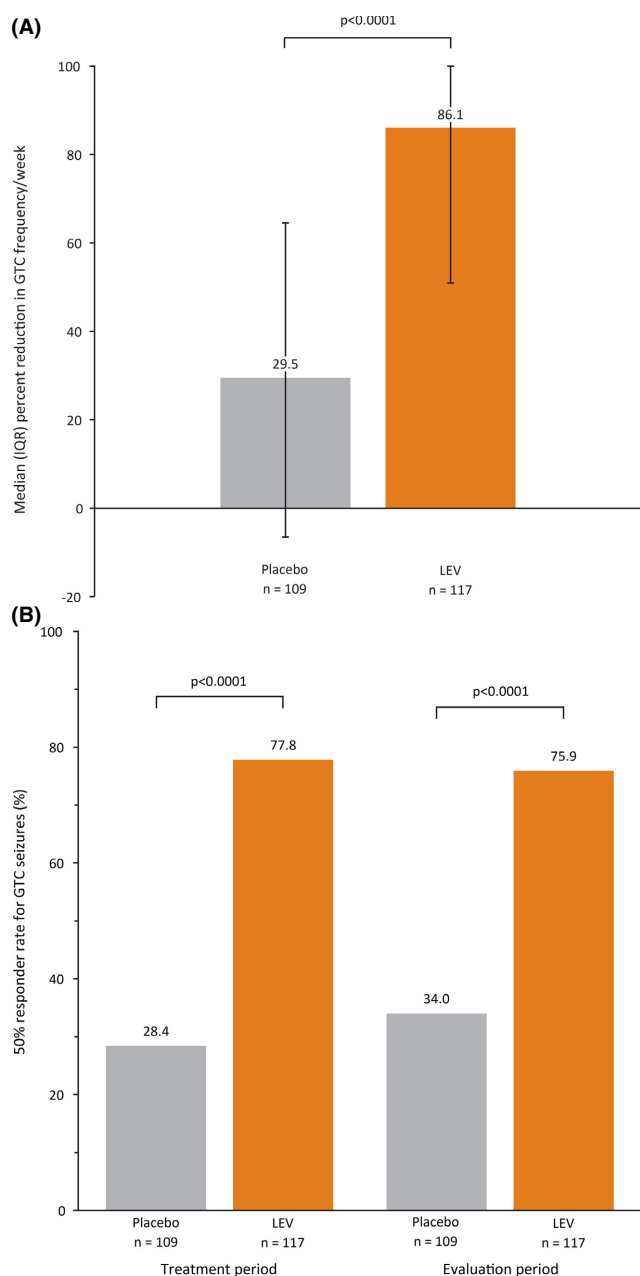


Figure 3.

A, Median percent reduction from combined baseline in generalized tonic-clonic seizures/week during the 16-week evaluation period; p-values versus placebo calculated using ANCOVA. **B,** Generalized tonic-clonic seizure 50% responder rates during the 28-week treatment and 16-week evaluation periods (full analysis set); p-values versus placebo calculated using logistic regression. ANCOVA, analysis of covariance; GTC, generalized tonic-clonic; IQR, interquartile range; LEV, levetiracetam.

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count (1.6% vs. 4.0%), decreased neutrophil count (0% vs. 3.2%), and somnolence (0.8% vs. 2.4%).

Of the TEAEs, 6/125 (4.8%) in the placebo group and 4/126 (3.2%) in the LEV group led to permanent

discontinuation of trial drug. In the placebo group, patients discontinued due to drowning (n = 2) and anxiety, decreased platelet count, epilepsy, and sudden unexplained death in epilepsy (SUDEP; all one patient each). In the LEV group, patients discontinued due to epilepsy, irritability, pregnancy, and psychotic disorder (all one patient each).

The incidence of serious TEAEs was low, with 4/125 (3.2%) reported in the placebo group and 1/126 (0.8%) reported in the LEV group. The 4 serious TEAEs in the placebo group were all reported for Chinese patients (drowning n = 2, epilepsy n = 1, and SUDEP n = 1) and the serious TEAE in the LEV group was pneumonia (reported for a Japanese patient).

In total, there were 3 deaths (2.4%) in the placebo group and none in the LEV group. Two patients in the placebo group died by drowning; neither death was thought to be related to trial drug. A Chinese patient in the placebo group died of SUDEP on day 87 of the evaluation period; this death was considered related to trial drug by the investigator.

Changes from baseline in hematology, blood chemistry, and vital signs were similar for the placebo and LEV groups. The most frequently reported TEAE related to clinical laboratory results was presence of protein in urine (placebo 0.8% vs. LEV 7.9%); all cases were mild in intensity and not considered clinically significant. All cases were reported in Chinese patients, with similar incidence during the dose-adjustment and evaluation periods. All cases resolved, apart from one case recorded as recovering/resolving. In 10/11 cases, the presence of protein in urine was considered related to trial medication by the investigator; however, in 9/11 cases, presence of protein in urine had also been detected during the baseline period prior to randomization. There were no clinically significant ECG findings.

Pharmacokinetics

Over the range of LEV doses studied (1,000–3,000 mg/day), the geometric mean LEV plasma concentration observed appeared to increase in proportion to the LEV dose (Table S1). Ranges of LEV plasma concentrations normalized to a dose of 500 mg were similar for Chinese and Japanese patients (data not shown).

DISCUSSION

In this double-blind, randomized, placebo-controlled trial of Chinese and Japanese patients with GTC seizures, treatment with adjunctive LEV 1,000–3,000 mg/day resulted in a significant reduction in GTC seizures/week during the 28-week treatment period versus placebo. Reduction in GTC seizure frequency occurred both in patients with idiopathic and symptomatic generalized epilepsy. In addition, the percent reduction from combined baseline in GTC seizures/week during the 16-week evaluation period, 50% responder rates during the treatment and evaluation periods, and

Table 2. Generalized tonic-clonic seizure freedom during the evaluation period (full analysis set)

	Overall		China		Japan	
	PBO (n = 109)	LEV (n = 117)	PBO (n = 97)	LEV (n = 103)	PBO (n = 12)	LEV (n = 14)
N ^a	97	108	87	97	10	11
Freedom from GTC seizures, n (%)	3 (3.1)	32 (29.6)	3 (3.4)	27 (27.8)	0	5 (45.5)
(95% CI)	0.6–8.8	21.2–39.2	0.7–9.7	19.2–37.9	0.0–30.8	16.7–76.6
p-Value		<0.0001		<0.0001		0.0351

CI, confidence interval; GTC, generalized tonic-clonic; LEV, levetiracetam; PBO, placebo.
^aNumber of subjects with at least one measurement during the period.

Table 3. Summary of TEAEs and incidence of most frequently reported TEAEs (safety population)

	Overall n (%)		China n (%)		Japan n (%)	
	PBO n = 125	LEV n = 126	PBO n = 104	LEV n = 104	PBO n = 21	LEV n = 22
Any TEAEs	65 (52.0)	72 (57.1)	50 (48.1)	52 (50.0)	15 (71.4)	20 (90.9)
Serious TEAEs	4 (3.2)	1 (0.8)	4 (3.8)	0	0	1 (4.5)
Drug-related TEAEs	17 (13.6)	30 (23.8)	12 (11.5)	21 (20.2)	5 (23.8)	9 (40.9)
Discontinuations due to TEAEs	6 (4.8)	4 (3.2)	5 (4.8)	2 (1.9)	1 (4.8)	2 (9.1)
Deaths	3 (2.4)	0	3 (2.9)	0	0	0
Incidence of TEAEs reported by ≥4% of patients in any treatment group						
Nasopharyngitis	20 (16.0)	24 (19.0)	14 (13.5)	18 (17.3)	6 (28.6)	6 (27.3)
Presence of protein in urine	1 (0.8)	10 (7.9)	1 (1.0)	10 (9.6)	0	0
Decreased platelet count	4 (3.2)	7 (5.6)	4 (3.8)	6 (5.8)	0	1 (4.5)
Pyrexia	5 (4.0)	7 (5.6)	5 (4.8)	3 (2.9)	0	4 (18.2)
Diarrhea	2 (1.6)	6 (4.8)	2 (1.9)	5 (4.8)	0	1 (4.5)
Headache	5 (4.0)	6 (4.8)	4 (3.8)	4 (3.8)	1 (4.8)	2 (9.1)
Constipation	1 (0.8)	5 (4.0)	0	2 (1.9)	1 (4.8)	3 (13.6)
GGT increased	1 (0.8)	5 (4.0)	1 (1.0)	5 (4.8)	0	0
Neutrophil count decreased	0	5 (4.0)	0	4 (3.8)	0	1 (4.5)
Weight decreased	3 (2.4)	5 (4.0)	3 (2.9)	4 (3.8)	0	1 (4.5)
Dizziness	9 (7.2)	4 (3.2)	8 (7.7)	4 (3.8)	1 (4.8)	0
Upper respiratory tract infection	5 (4.0)	4 (3.2)	5 (4.8)	4 (3.8)	0	0

GGT, γ -glutamyltransferase; LEV, levetiracetam; PBO, placebo; TEAEs, treatment-emergent adverse events.
 Assessment for PBO and LEV ranges from start of dose adjustment period to end of evaluation period.

freedom from GTC seizures and all seizure types during the evaluation period were all greater for the LEV group compared with the placebo group.

Results for the primary efficacy variable in the Chinese and Japanese trial populations were similar, although the trial was not designed with statistical power to demonstrate differences in efficacy by country.

The efficacy data compare favorably with those from the similarly designed trial, N01057, which was conducted in Europe, North America, Mexico, Australia, and New Zealand.¹² The mean percent reduction in GTC seizures/week in the current trial was 12.6% with placebo and 68.8% with LEV, compared with 28.2% and 56.5%, respectively, for trial N01057.¹² Trial N01057 enrolled only patients with idiopathic generalized epilepsy, whereas in the current trial both patients with idiopathic generalized epilepsy and patients with symptomatic generalized epilepsy, cryptogenic generalized epilepsy, or undetermined epilepsy were

eligible for inclusion if they had GTC seizures. In LEV-treated patients, the median percent reduction from combined baseline in GTC seizures/week during the treatment period was similar for patients with idiopathic generalized epilepsy (73.9%) and those with symptomatic generalized epilepsy (78.7%). Therefore, the expansion of the patient population to include patients with symptomatic generalized epilepsy, cryptogenic generalized epilepsy, or undetermined epilepsy does not appear to have affected the efficacy of LEV on GTC seizures. In this trial, among those patients with idiopathic generalized epilepsy, a high proportion were recorded as having other idiopathic epilepsies, with only 6 patients having juvenile myoclonic epilepsy and 8 patients having epilepsy with grand mal seizures on awakening. The results of this study are therefore informative for the clinician treating the wider idiopathic generalized epilepsy population. Of patients from 2 large cohort studies classified as having idiopathic generalized epilepsy, 30.0% and 55.6% were reported

as having “other idiopathic generalized epilepsies” in which syndromes were not clearly individualized.²⁶

Safety and tolerability findings in this population of Chinese and Japanese patients with uncontrolled GTC seizures demonstrated that LEV was well tolerated. The most frequently reported TEAEs were nasopharyngitis, presence of protein in urine, decreased platelet count, and pyrexia. There were no drug-related reports of nasopharyngitis. Drug-related presence of protein in urine was more frequent in the LEV group versus the placebo group; however, all cases were mild in intensity, and in 9 of 11 cases protein in urine had been detected during baseline (these were not considered to be clinically significant). It was not clear why protein in urine was reported more frequently in this population compared with the N01057 trial. The incidence of serious TEAEs was low. In total, 3 patients died, 2 due to drowning and one due to SUDEP (considered related to study medication); all had belonged to the placebo group. TEAEs were broadly consistent in incidence and type with those reported in the N01057 trial,¹² although presence of protein in urine, decreased platelet count, and pyrexia were more frequently reported in the current trial. In contrast, TEAEs such as irritability and mood swings were reported at higher incidences in the N01057 trial (irritability: placebo 2.4%, LEV 6.3%; mood swings: placebo 1.2%, LEV 5.1%)¹² than in the current trial (irritability: placebo 0%, LEV 1.6%; mood swings: placebo 0%, LEV 0%). Completion rates were relatively low (placebo 48.0% vs. LEV 64.3%), with most patients discontinuing due to lack of efficacy (placebo 32.0% vs. LEV 21.4%). Completion was lower than in the N01057 trial, where completion rates were placebo 83.3% versus LEV 87.5%.¹² In the current trial, patients who were on a stable dose of LEV for ≥ 8 weeks who discontinued due to lack of efficacy had the option to receive open-label LEV, which may have affected completion rates. This option had been intended for patients randomized to placebo, but due to the double-blind nature of the trial, patients who did not respond from either treatment group were offered this option.

A trial of single-dose LEV in Chinese healthy volunteers showed that the PK of LEV 500–1,500 mg was dose-proportional and in line with historical PK data from Caucasian patients.²⁷ In addition, population PK modeling of LEV in Japanese and Western adults suggested that differences between the populations appeared to arise from body weight and not from ethnicity.²⁸ Finally, a PK trial of intravenous LEV in healthy Japanese and Caucasian volunteers concluded that their PK profiles were similar.²⁹ Consistent with these previous trials, LEV plasma concentrations obtained in the current trial appeared to be dose-proportional.

For patients with newly diagnosed or untreated GTC seizures, ILAE guidelines note that class III evidence is available for the possible effectiveness/efficacy of carbamazepine, lamotrigine, oxcarbazepine, phenobarbital,

phenytoin, topiramate, and valproate as initial monotherapy, and potential effectiveness/efficacy of LEV, gabapentin, and vigabatrin. Further, the authors observe that carbamazepine may not be an optimal treatment for GTC seizures; indeed some class IV evidence suggests that carbamazepine and phenytoin may precipitate GTC seizures.³ However, patients taking part in the trials used for the development of these evidence-based guidelines were largely from Western populations. In contrast, a survey of 49 experts in tertiary hospitals in China identified valproate as the treatment of choice for initial monotherapy and lamotrigine as second monotherapy for patients with idiopathic generalized epilepsy, whereas topiramate and LEV were treatments of choice for patients with idiopathic generalized epilepsy and concomitant hepatitis B.³⁰ Clinical guidelines from the Japanese Society of Neurology in 2010 also recommend valproate for monotherapy in new-onset generalized epilepsy.³¹

Conducting trials in populations with different genetic make-up may identify differences in safety and tolerability. For example, the human leukocyte antigen allele HLA-B*1502, commonly found in people of Han Chinese origin, is strongly associated with a risk of serious and life-threatening cutaneous reactions during treatment with carbamazepine.³² Genetic polymorphisms in cytochrome P450 (CYP) enzymes may also affect drug metabolism, although because LEV is not extensively metabolized by the liver, with 66% of the dose remaining unchanged in the urine,³³ this concern is of lesser importance in trials evaluating LEV.³⁴ The PK profile of LEV, together with the favorable efficacy and safety profile demonstrated in the present trial, suggest that LEV may be a suitable treatment for GTC seizures in Japanese and Chinese patients.

Trial limitations include the relatively short duration for assessing treatment of a chronic disease, potential errors in reporting seizures and adverse events by patients and/or their caregivers, and protocol deviations reported. As with any clinical trial, patients were selected according to pre-specified inclusion criteria, which may limit the generalizability of the findings. The trial design allowed evaluation of LEV 1,000 and 3,000 mg/day; however, it should be acknowledged that the design favors efficacy because a more realistic dose escalation might be from 1,000 to 2,000 mg/day, instead of directly to 3,000 mg/day. Finally, it should also be noted that the duration of the dose-adjustment period was fixed, as was the final dose of LEV; it is possible that patients could tolerate higher doses of LEV if they were increased more gradually over a longer period of time.

In conclusion, in this double-blind, randomized trial, adjunctive LEV 1,000–3,000 mg/day was effective in reducing GTC seizure frequency in Chinese and Japanese patients ≥ 16 years old with GTC seizures uncontrolled by 1–2 AEDs. Seizure reduction occurred both in patients with idiopathic and symptomatic generalized epilepsy. LEV was well tolerated in this population.

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DISCLOSURE OF CONFLICT OF INTEREST

LW, KY, YI, YO, and MS received personal fees from UCB Pharma while the study was being conducted. ZH, XW, and DZ have nothing to disclose. KT received personal fees from UCB Pharma while the study was being conducted and personal fees from UCB Pharma, Otsuka Pharmaceutical Co. Ltd, and GlaxoSmithKline outside the submitted work. XD, YM, and TS are employees of UCB Pharma. All authors disclose medical writing support, which was funded by UCB Pharma. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. LEV plasma concentrations over time after dosing (PK-PPS population).

Figure S1. Study design.