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A randomized, double-blind, double-dummy, multicenter trial comparing the efficacy and safety of extended- and immediate-release levetiracetam in people with partial epilepsy

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Data Access and Responsibility: The principal investigator, Tony Wu, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Highlights

- LEV-ER is equivalent in reducing the frequency of partial onset seizures to LEV-IR.
- LEV-ER add-on therapy can be well-tolerated in patients with uncontrolled epilepsy.
- Most of the adverse events related to LEV-ER were mild in severity, and resolved.
- The overall quality of life was significantly improved in the LEV-ER group.

Abstract

Purpose:

The aim of this trial was to compare the efficacy and safety of two formulations of levetiracetam in people with partial epilepsy over a 12-week treatment period.

Methods:

We performed a randomized, paralleled, and multicenter trial that consisted of a 4-week single-blind placebo run-in, followed by a 12-week double-blind, double-dummy treatment phase to compare the efficacy and safety of levetiracetam extended-release (LEV-ER) and immediate-release (LEV-IR) tablets as an adjunctive treatment in adult patients with uncontrolled epilepsy.

Results:

The median partial-onset seizure (POS) frequency per week (min-max) was 0.3 (0.0, 17.4; 95% confidence interval [95% CI] 1.3, 4.8) in the LEV-ER group and 0.3 (0.0, 31.4; 95% CI −0.1, 4.3) in the LEV-IR group. No serious adverse events occurred during the trial period. Both groups had the same responder rate (58.6%), while a higher rate of seizure freedom over the treatment period was noted in the LEV-ER group compared with the LEV-IR group (27.6% vs. 13.8%, respectively). The European Quality of Life–5 Dimensions scores significantly increased in the LEV-ER–treated group, in contrast to the scores in the LEV-IR group, which decreased (7.2 vs. −1.5, $p = 0.03$).

Conclusion:

These results suggest that LEV-ER is equivalent to LEV-IR in reducing the frequency of POS and has a similar tolerability as LEV-IR as an add-on therapy. In addition, LEV-ER treatment improved the health-related quality of life of people with uncontrolled partial epilepsy.

Abbreviations: AE, adverse event; LEV-ER, levetiracetam extended-release; LEV-IR, levetiracetam immediate-release; ITT, intention-to-treat; n, number; PP, per protocol.

Keywords: Levetiracetam extended-release; Partial epilepsy; Uncontrolled epilepsy; Partial-onset seizures; Adjunctive treatment

Introduction

Epilepsy is a serious chronic neurological condition characterized by recurrent seizures, which have significant impacts on both health and quality of life of affected individuals. For people with epilepsy, adherence to antiepileptic drug (AED) regimens is crucial for seizure control and can maximize the quality of life [1]. Nonadherence may result in breakthrough seizures with serious consequences that may also compromise an individual's perceived quality of life [2].

Previous studies on patients with epilepsy have indicated that drug compliance declined in accordance with more frequent dosing intervals, and missing doses are associated with the occurrence of seizure [3, 4]. On the other hand, reduced daily dosing is associated with improved compliance [5]. Levetiracetam extended-release (LEV-ER) formulation was developed to provide patients with a more convenient once-daily dosing option [6]. The once-daily 1,000-mg dose of LEV-ER has been demonstrated to be bioequivalent to two 500-mg doses of the immediate-release levetiracetam (LEV-IR) given 12 hours apart [7]. This once-daily dosing option allows patients to more easily adhere to their AED medications in their daily routine, thereby minimizing the chance of missing doses. Although some concerns have been raised about more serious effects (e.g., breakthrough seizure) because of the shorter forgiveness period of the extended-release formulation, Pellock and Brittain, using computer simulations, found that the forgiveness interval of the extended-release formulation was longer (ER once daily) or similar (ER twice daily) to the IR formulation of 3 times daily [8].

In a recent meta-analysis of 10 randomized, placebo-controlled trials of add-on LEV treatment in people with incomplete seizure control that assessed the adverse effects associated with LEV therapy, favorable efficacy and safety profiles of LEV were found for both IR and ER formulations [9]. However, a direct comparison between the IR and ER formulations of LEV has not been reported.

Our trial aimed to compare the efficacy, safety, tolerability, and changes in quality of life between the LEV-ER and LEV-IR formulations after 12 weeks of treatment in people with poorly controlled partial seizures. This trial provides evidence of noninferiority of efficacy, safety, and tolerability by using LEV-ER in comparison with LEV-IR in people with uncontrolled partial seizures.

Materials and methods

Trial design

This trial was designed as a prospective, double-blind, double-dummy, randomized and paralleled, active-controlled multicenter trial, comparing the efficacy, safety, and tolerability of once-daily LEV-ER add-on therapy relative to twice-daily LEV-IR therapy in people with inadequate control of partial seizures. The trial was conducted in five medical centers in Taiwan between March 2013 and December 2014 and consisted of a 4-week single-blind placebo run-in baseline period, followed by a 12-week double-blind and double-dummy trial treatment period.

During the 4-week run-in baseline period, subjects had to be on a stable dose of one or more AEDs and experienced two or more partial-onset seizures (POS), with or without secondary generalization. Partial seizures were classified according to the Commission on the Classification and Terminology of the International League against Epilepsy [10].

After the run-in baseline period, eligible patients were randomized into one of the two comparative groups. Patients in the LEV-ER group were treated with two tablets of 500 mg LEV-ER in the morning and one placebo tablet in the evening. Patients in the LEV-IR control group were treated with one tablet of 500 mg LEV-IR and one placebo tablet in the morning and one tablet of 500 mg LEV-IR in the evening.

A randomization code list was generated using permuted blocks to ensure the balance between the study groups by an independent biostatistician who was not involved in the trial. After confirming the eligibility at and during the baseline period, patients were given a unique randomization number and were randomly assigned to one of the two treatment groups in a 1:1 ratio accordingly at each participating center. During the whole trial period, randomization data were not accessible by anyone involved in the trial. The investigators, research coordinators, patients, and their families were all blind to treatment allocation.

Participants

All patients at least 16 years of age with medically refractory partial epilepsy with or without secondary generalization were screened for inclusion at the neurologic clinics. Eligibility was limited to patients taking one or more AEDs at a stable dosage for more than 4 weeks prior to screening and who experienced two or more seizures during the 4-week run-in baseline period. Patients were excluded from the trial if they had ever taken LEV or met any of the following conditions: hypersensitivity to LEV, status epilepticus within the past 3 months, progressive brain lesion, active central nervous system (CNS) infection, pseudoseizures, conversion disorders or other nonepileptic events, constant suicidal ideation, or attempted suicide. Additional exclusion criteria included impaired renal function, unstable dosage of any CNS medication, pregnancy, or lactation.

The trial was conducted in compliance with the ethical principles of the Declaration of Helsinki and was consistent with the International Conference on Harmonization Good Clinical Practice guidelines. The Ethics Committee approved the trial at each study center. All patients provided written informed consent.

Outcomes evaluation

The primary endpoint was the frequency of POS per week over the 12-week treatment period. The key secondary endpoints included safety, tolerability, and impact on quality of life.

Efficacy assessments

Each patient was required to record their seizures on a diary card. The primary efficacy outcome measure was the frequency of POS per week over the trial treatment period. Important secondary efficacy endpoints included responder rate (defined as the proportion of patients with a ≥50% reduction in seizure frequency per week from baseline) and the percentage reduction from baseline, documenting seizure freedom over the entire 12-week treatment period, and categorized response.

Safety and tolerability assessments

Safety analyses were based on changes in vital signs, body weight, physical and neurologic examination results, laboratory values, the Hospital Anxiety and Depression Scale (HADS), the Columbia Suicide Severity Rating Scale (C-SSRS), and treatment-related adverse events (AEs). Treatment-related AEs were recorded, coded, extracted, and analyzed using the Medical Dictionary for Regulatory Activities. Discontinuation of treatment was assessed to determine the tolerability of the trial medication.

Quality-of-life assessment

We employed both the Quality of Life in Epilepsy Inventory-31-P (QOLIE-31-P) to assess the health-related quality of life of patients with epilepsy and the European Quality of Life–5 Dimensions (EQ-5D) to evaluate the patient's overall health outcome and to further complement other quality-of-life questionnaires to assess the full range of treatment outcomes for each treatment option. The QOLIE-31-P assesses health-related quality-of-life outcomes for adults with epilepsy. The overall score and subscale score range from 0 to 100, with higher scores representing better life quality [11, 12]. Patients' feelings regarding epilepsy within the past 4 weeks were categorized into different domains, including seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive and medication effects, and social function. In addition, the degree of distress to each domain was also assessed to reflect patients' worries about epilepsy. The distress score also ranged from 0 to 100, with higher scores reflecting greater distress. The EQ-5D questionnaire consists of two components. The first component evaluates five dimensions, including mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression, and each dimension defines three levels of severity as no problems, some problems, and extreme problems. The other component is the patient's self-rated health on a vertical visual analogue scale (VAS), with a higher VAS score indicating better quality of life [13, 14]. Both questionnaires were assessed by a well-trained and qualified site staff at baseline and at the end of the study visits. Patients were asked to complete the questionnaires by themselves.

Statistical analyses

We determined that a sample size of 61 patients per group would have 80% power to detect a difference in log-transformed seizure frequency per week, with a mean frequency of 0.025 and standard deviation of 0.4 based on the previous study results of LEV-ER and LEV-IR over placebo separately. This level of detection is equivalent to a noninferiority margin of −0.18 in seizure frequency per week, assuming a one-sided *t*-test at a significance threshold of 0.025 [6, 15-20]. Considering a 20% dropout rate, a goal of 154 patients was planned for this trial.

Efficacy analyses were performed in the per-protocol (PP) population comprising all randomized patients who had completed 12 weeks of treatment without major protocol violations. Safety analyses were summarized using the intention-to-treat (ITT) population, which was defined as subjects who took at least one trial medication and had at least one postbaseline measurement.

Descriptive statistics were calculated for all efficacy and safety variables. Seizure frequency was presented as the weekly median per patient along with minimum and maximum frequencies, while the percentage reduction was presented as the mean and standard deviation (SD). The difference in the POS frequency per week between the two groups was conducted by a two-sample *t*-test. The change from baseline and percentage change from baseline in seizure frequency at week 12 were compared between trial treatment groups using the Wilcoxon rank-sum test. The 50% responder rate and categorical responses of changes in weekly seizure frequency between treatments over the treatment period were compared using the chi-square test. All statistical assessments were two-tailed, with significance defined as p values < 0.05, using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Eighty-four patients were screened for inclusion (Fig. 1), of which 16 patients were excluded because they either did not meet inclusion criteria or they fulfilled one or more exclusion criterion. The remaining 68 patients were randomized into either the LEV-ER (n = 34) or LEV-IR (n = 34) groups. Of these 68 patients, one patient in the LEV-IR group was excluded for further evaluation because of loss to follow-up. The cohort with 34 patients in the LEV-ER and 33 patients in the LEV-IR were defined as the ITT groups. Seven patients (five on LEV-ER and two on LEV-IR) withdrew from the trial prior to completion, and 2 patients receiving LEV-IR violated the

enrollment criteria and were excluded from the PP population. Consequently, 29 patients in the LEV-ER group and 29 in the LEV-IR group who completed the trial composed the PP population. No differences in patient demographics or seizure type were evident between the PP population groups (Table 1). At baseline, at least two AEDs were taken by 72.4% of subjects in the LEV-ER group and 62.1% of subjects in the LEV-IR group, respectively. There was no statistical difference in the number of baseline AEDs used between the two groups by Fisher's exact test (*p* = 0.27).

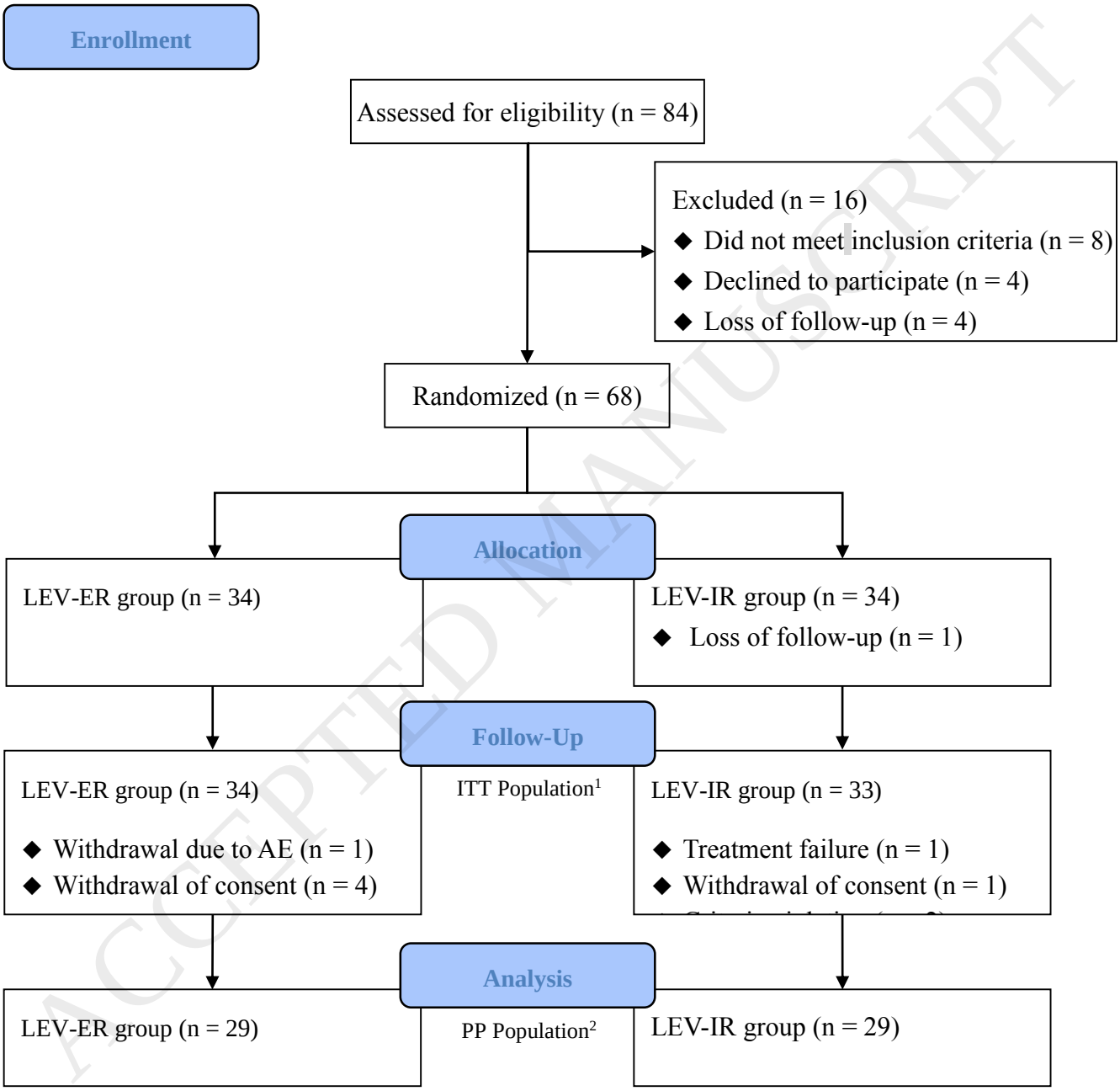

Figure 1. Summary of patient disposition flowchart[1].The ITT population consisted of all randomized patients taking at least one study medication with at least one postbaseline measurement.

[2.]The PP population included all patients completing the 12-week treatment, excluding those who had a major protocol deviation.

Abbreviations: AED, antiepileptic drug; LEV-ER, levetiracetam extended-release; LEV-IR, levetiracetam immediate-release; Min-max, minimum-maximum; n, number; PP, per protocol; SD, standard deviation.

Efficacy

The primary endpoint was POS frequency per week over the 12-week treatment period. At baseline, the median POS frequency per week in the PP population was 1.0 in the LEV-ER group and 0.8 in the LEV-IR group (Table 2). At the end of the 12-week treatment period, the median POS frequency per week had decreased to 0.3 in both groups (95% confidence interval [CI]: 1.3, 4.8 in the LEV-ER versus 95% CI: −0.1, 4.3 in the LEV-IR, $p = 0.40$).

In the LEV-ER group, the percentage seizure change over the treatment period was −48.0% ± 49.8%, compared with −45.9% ± 41.6% in the LEV-IR group ($p = 0.86$). The responder rate (≥50% reduction) over the 12-week treatment period was 58.6% in both groups ($p > 0.99$). The seizure freedom rate over the entire 12-week maintenance period was 27.6% in the LEV-ER group versus 13.8% in the LEV-IR group ($p = 0.19$). In summary, the percentage reduction in POS and rate of seizure-free status across the treatment period were slightly higher in the LEV-ER group than in the LEV-IR group, although no statistical significance was detected.

Abbreviations: LEV-ER, levetiracetam extended-release; LEV-IR, levetiracetam immediate-release; Min-max, minimum-maximum; n, number; POS, partial-onset seizures; PP, per protocol.

Baseline period is the 4-week run-in period.

The percentage change in POS frequency from baseline over the treatment period was analyzed categorically, with a positive response indicating a reduction in POS frequency (Fig. 2). More than half of the patients in both groups reported a seizure reduction of at least 50% in response to trial treatment. Both groups had the same proportion of patients who reported improvement in seizure frequency of at least 25% ($p = 0.88$).

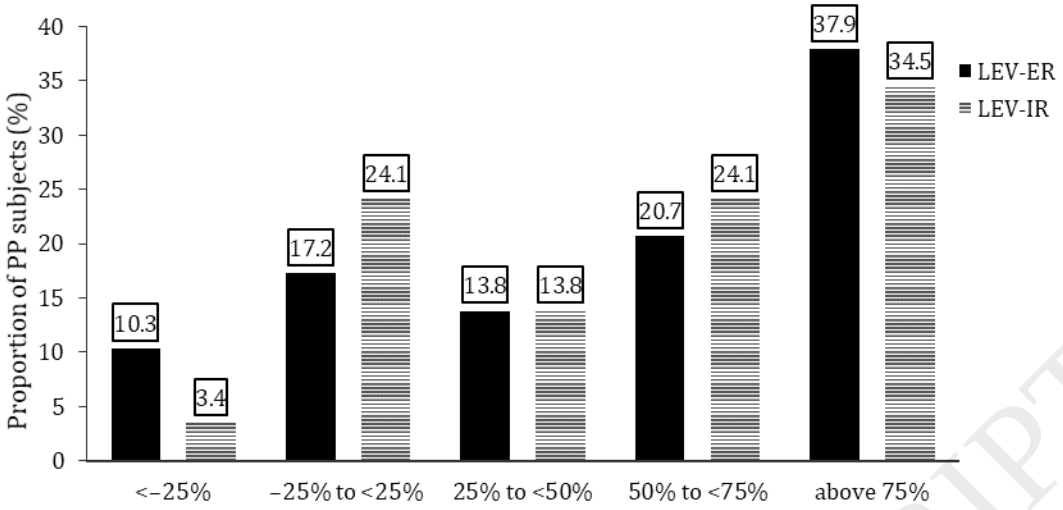

Figure 2. Changes in the percentage of seizure frequency over the treatment period.

Abbreviations: LEV-ER, levetiracetam extended-release; LEV-IR, levetiracetam immediate-release; PP, per protocol.

Safety and tolerability

Safety monitoring included laboratory values, physical and neurologic examination results, vital signs, body weight, the HADS, the C-SSRS, and AEs.

Over the course of this trial, no significant differences in the HADS, C-SSRS, or laboratory findings were observed between the groups. For the HADS, changes in anxiety were similar between groups (0.2 ± 2.5 in the LEV-ER vs. 0.1 ± 3.4 in the LEV-IR, $p = 0.93$), while a greater decrease in the HADS depression score was observed in the LEV-ER group, although the difference did not reach statistical significance (−0.7 ± 2.8 in the LEV-ER group vs. −0.1 ± 3.1 in the LEV-IR group, $p = 0.43$). With regard to laboratory assessments, no significant changes in hematology, biochemistry, vital signs, or physical examinations were noted during the trial period.

Treatment-relevant AEs were experienced in six patients (17.6%) taking LEV-ER medication and in four patients (12.1%) taking LEV-IR medication (Table 3). Most of the treatment-related AEs were considered mild in severity, and no serious AEs were reported from either treatment group. Two patients (5.9%) from the LEV-ER group complained of memory impairment, which was not noted in patients receiving LEV-IR. Other neuropsychiatric events, including disturbance in attention, emotional disorder, psychotic disorder, mood altered, and communication disorder each occurred in one patient from the LEV-ER group, with an incidence rate of 2.9%. Somnolence was observed in both groups, with each occurring in one patient in the LEV-ER and LEV-IR groups, respectively. No new safety concerns were raised

during the trial period. With regard to the tolerability of the study treatment, one patient in each group terminated the study treatment prematurely. One patient experienced poor emotional control leading to discontinuation of LEV-ER, but this event was mild in severity, whereas one patient discontinued LEV-IR due to lack of efficacy. Overall, most of the patients tolerated LEV treatment well.

Abbreviations: AE, adverse event; LEV-ER, levetiracetam extended-release; LEV-IR, levetiracetam immediate-release; n/No., number.

Quality of life

The change from baseline in the QOLIE-31-P score was 2.4 ± 10.1 for patients receiving LEV-ER compared with 1.5 ± 13.2 for LEV-IR in the PP population; this difference was not statistically significant (Table 4). A slight decrease in the distress score of the QOLIE-31-P (−1.0 ± 12.9) was observed in the LEV-ER group, compared with an increase in the LEV-IR group (2.5 ± 15.5) without statistical significance. The EQ-5D score increased in the LEV-ER-treated group but showed a significantly negative trend in the LEV-IR group (7.2 ± 18.9 vs. −1.5 ± 15.3, $p = 0.03$), suggesting improvements in the health status of the patients in the LEV-ER group. In summary, these results showed that the quality of life as assessed by the EQ-5D among patients in the LEV-ER group significantly improved.

Abbreviations: EQ-5D, European Quality of Life–5 Dimensions; LEV-ER, levetiracetam extended-release; LEV-IR, levetiracetam immediate-release; Min-max, minimum-maximum; n, number; QOLIE-31-P, Quality of Life Epilepsy Inventory-31-P; PP, per protocol; VAS, visual analog scale.

*$p < 0.05$.

Discussion

Previous studies [17, 18, 21-25] investigated immediate- and extended-release formulations of LEV individually and compared their efficacy and safety indirectly. Our trial is the first to compare directly the efficacy and safety of once-daily LEV-ER and twice-daily LEV-IR as add-on therapies in patients with POS. Our findings suggest that LEV-ER is a favorable option for the treatment of patients with partial epilepsy. Given the added benefit of improved adherence with once-daily dosing [17], LEV-ER may be more beneficial than LEV-IR for patients with POS.

LEV has been shown to be effective and well tolerated by patients with refractory partial seizures at doses of 1,000 to 3,000 mg per day [15-18]. The response rates of the LEV-ER and LEV-IR groups were the same (58.6%) in our 12-week treatment regime and higher as compared with studies conducted in Finland [17] and Taiwan [18], although our higher response rate may be explained by the low frequency of POS at baseline. Our findings at the

medium-to-low daily dose (1,000 mg/day) are comparable with those of a previous long-term study (12-month treatment at a mean dose of 1,235.5 mg/day) [24] and a retrospective observational study (24-week treatment at a mean dose of 1,167 mg/day with an efficacy threshold of ≥50% reduction in seizure frequency) in Asian patients [26]. Furthermore, we found a consistent positive effect of LEV on seizure freedom during the evaluation period [15, 16, 18, 19], particularly in patients treated with LEV-ER (27.6% vs. 13.8%, $p = 0.19$). Thus, although our sample size was small, our results were consistent with those of previous studies, suggesting that a 1,000-mg/day dose of LEV is effective as an add-on therapy in patients with uncontrolled partial seizures. Nevertheless, future prospective dose-response studies with large patient populations are warranted to clarify the effects of higher doses of LEV-ER and LEV-IR.

The effects of seizure control on quality of life in patients with epilepsy are well-documented [1]. Our significant changes in the EQ-5D health outcomes were evident over the treatment period, such that health scores increased in the LEV-ER group and decreased in the LEV-IR group relative to baseline. Although with the nonsignificant changes in QOLIE-31-P and HADS in our trial, these findings are similar to those reported by Cramer et al. [11], who evaluated changes in quality of life during long-term treatment with LEV and concluded that distress was lower when the health-related quality of life was higher. Furthermore, our findings are consistent with those of Hagemann et al. [27], who reported positive effects on both QOLIE-31 and HADS scores. Moreover, Hagemann and the study team found that the change in seizure frequency was significantly associated with the HADS depression subscale score and concluded that add-on therapy with LEV improved health-related quality of life, anxiety, and depression in responders (≥50% seizure reduction). Although we did not assess the relationship between seizure frequency and quality-of-life–related outcomes, the findings of previous studies provide ample evidence of the positive effects of LEV-ER treatment on seizure freedom and quality of life.

With respect to safety outcomes, nervous system disorders were the most commonly reported AEs relevant to treatments; however, we observed no clinically relevant differences in overall AEs, withdrawals due to AEs, or serious AEs between groups in our head-to-head study. The higher percentage of AEs observed in the LEV-ER group may be attributable to the morning rather than evening dosing protocol. Psychiatric AEs were observed in three patients receiving LEV-ER; however, none of these events was considered severe. Furthermore, no suicidal ideation or behavior was reported. Half of the events were resolved before the patients completed the trial treatment. Chung et al. [22] reported similar psychiatric AEs associated with LEV-ER treatment at once-daily doses of 1,000 and 2,000 mg. In contrast, a meta-analysis conducted by Richy et al. [23] found that patients taking LEV-XR (1,000 mg once daily)

experienced fewer psychiatric disorders than those taking LEV-IR (500 mg twice daily). However, our small sample size prevented a conclusive comparison of the frequency of AEs associated with the LEV-ER and -IR formulations. Although the relatively constant plasma concentration of the ER formulation may minimize concentration-related AEs, psychiatric disorders may still occur. Thus, the effect of the ER formulation of LEV on psychiatric outcomes warrants further study in a larger population. The fact that several studies have found the 1,000-mg daily dose of LEV to be an effective add-on therapy diminishes the concerns about AEs. Taken together, the findings on seizure control, health status, emotion control, and safety support the use of LEV-ER as an alternative add-on therapy for patients with POS.

Minimizing plasma drug fluctuations and improving compliance are important in the clinical management of patients with seizure disorders. We did not collect blood samples to compare the fluctuation index between the LEV-ER and LEV-IR formulations; however, Rouits et al. [7] reported that the plasma fluctuations were comparable. Although the fluctuation index of LEV is higher than that of other AEDs [28], a previous meta-analysis found that the outcomes of add-on therapy with LEV were favorable in terms of responder and withdrawal rates [29]. Moreover, LEV is effective as a monotherapy in patients with refractory or partial seizures [30]. The other advantages of LEV include absence of AEs related to liver function, rapid onset of action, and safety of intravenous loading.

A previous study had observed a slightly higher seizure-free rate over the 6-month treatment in patients receiving only one concomitant AED other than LEV (immediate-release formulation) as compared with the overall analyzed patients and concluded that it was possibly due to the lower refractory rate in this subgroup [31]. In our study, the median POS and responder rate during the treatment were the same in the two groups, while the seizure-free rate in the LEV-ER group was higher than that in the LEV-IR group, despite a greater percentage of patients taking more than three AEDs in the LEV-ER group. Another study by Gidal et al. suggested that LEV did not affect the serum concentrations of concomitant AEDs at steady state [32]. This may indicate that LEV-ER effectively controls the seizure episodes through the constant plasma level of LEV-ER based on the pharmacokinetic properties and synergistic interactions with other concomitant AEDs without changing the plasma concentration of these AEDs. As a result, the quality of life improved in patients on LEV-ER. Summarizing the above, the observations from previous studies support the efficacy of LEV as a treatment option for seizures.

Enrolling patients in our trial was not easy because seizures affect both the health and quality of life, and patients are willing to undergo treatments that may reduce symptoms and improve activities of daily living. Therefore, the main limitation of our trial was the small

sample size, which resulted in insufficient power to conclude noninferiority of LEV-ER compared with LEV-IR, while small differences in efficacy between the two groups for the treatment of POS were observed. Furthermore, because of the double-dummy design, which required twice-daily dosing, we were unable to observe the improvement in adherence associated with once-daily dosing. Therefore, further study of dosing-related effects in an extended open-label study is needed.

Conclusions

This first head-to-head trial suggests that LEV-ER treatment as a once-daily add-on to existing AED regimens in patients with uncontrolled POS is similar to LEV-IR in terms of efficacy and improvements in health-related quality of life. The safety and tolerability profiles of the LEV-ER group were similar to that of the LEV-IR group.

Conflict of Interest

Funding for the trial was provided by Lotus Pharmaceutical Co., Ltd. None of the authors have any conflict of interest to disclose. 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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Table 1. Demographic characteristics

Characteristic	PP population LEV-ER (n = 29)	PP population LEV-IR (n =29)	*p*-value
Age (years)			0.58
Mean ± SD	38.1 ± 12.2	39.9 ± 13.0	
Min-max	(18.0, 62.4)	(20.6, 64.8)	
Gender			0.19
Female, n	11	16	
Male, n	18	13	
Body weight (kg)			0.19
Mean ± SD	67.9 ± 13.8	62.8 ± 15.0	
Min-max	(41.0, 92.6)	(42.0, 100.0)	
History of seizure type			
Simple partial seizure, n	10	4	0.07
Complex partial seizure, n	19	21	0.57
Partial seizure evolving to secondarily generalized seizures, n	13	11	0.59
AED			0.27
1	8 (27.6%)	11 (37.9%)	
2	10 (34.5%)	12 (41.4%)	
3	11 (37.9%)	5 (17.2%)	
>3	0 (0.0%)	1 (3.4%)	

Table 2. Efficacy evaluation

	PP population		
Characteristic	LEV-ER (n = 29)	LEV-IR (n = 29)	*p*-value
Median POS frequency per week			
Baseline (min-max)	1.0 (0.3, 29.8)	0.8 (0.3, 26.5)	0.17
Treatment period (min-max)	0.3 (0.0, 17.4)	0.3 (0.0, 31.4)	0.40
95% CI	(1.3, 4.8)	(−0.1, 4.3)	
% reduction from baseline over the treatment period			0.86
Mean ± SD	−48.0 ± 49.8	−45.9 ± 41.6	
95% CI	(−66.9, −29.1)	(−61.7, 30.1)	
Responder rate over the treatment period			>0.99
≥50%, n (%)	17 (58.6%)	17 (58.6%)	
Seizure free at week 12			>0.99
Seizure-free rate, n (%)	17 (58.6%)	16 (55.2%)	
Seizure free during the treatment period			0.19
Seizure-free rate, n (%)	8 (27.6%)	4 (13.8%)	
Days of being seizure free per 4 weeks			0.22
Mean ± SD	20.9 ± 8.9	23.9 ± 6.8	
95% CI	(17.5, 24.3)	(21.4, 26.5)	

Table 3. Summary of AEs related to the study drug in the ITT population

Characteristic	LEV-ER	LEV-IR
No. of patients	34	33
No. of patients with treatment-related AEs, n (%)	6 (17.6%)	4 (12.1%)
No. of treatment-related AEs	13	8
No. of patients with treatment-related AEs by severity[&]		
Mild	5	4
Moderate	1	1
No. of treatment-related AEs by severity		
Mild	12	6
Moderate	1	2
Gastrointestinal disorder, No. of patients (%)	**2 (5.9%)**	**1 (3.0%)**
Mouth ulceration	0 (0.0%)	1 (3.0%)
Constipation	0 (0.0%)	1 (3.0%)
Nausea	1 (2.9%)	0 (0.0%)
Hypoesthesia oral	1 (2.9%)	0 (0.0%)
General disorders and administration site conditions, No. of patients (%)	**1 (2.9%)**	**1 (3.0%)**
Fatigue	1 (2.9%)	1 (3.0%)
Infections and infestations, No. of patients (%)	**1 (2.9%)**	**0 (0.0%)**
Upper respiratory tract infection	1 (2.9%)	0 (0.0%)
Injury, poisoning, and procedural complications, No. of patients (%)	**0 (0.0%)**	**1 (3.0%)**
Head injury	0 (0.0%)	1 (3.0%)
Lip injury	0 (0.0%)	1 (3.0%)
Nervous system disorders, No. of patients (%)	**3 (8.8%)**	**2 (6.1%)**
Disturbance in attention	1 (2.9%)	0 (0.0%)
Dizziness	1 (2.9%)	1 (3.0%)
Memory impairment	2 (5.9%)	0 (0.0%)

Characteristic	LEV-ER	LEV-IR
Somnolence	1 (2.9%)	1 (3.0%)
Psychiatric disorders, No. of patients (%)	**3 (8.8%)**	**0 (0.0%)**
Emotional disorder	1 (2.9%)	0 (0.0%)
Psychotic disorder	1 (2.9%)	0 (0.0%)
Mood altered	1 (2.9%)	0 (0.0%)
Communication disorder	1 (2.9%)	0 (0.0%)
Renal and urinary disorders, No. of patients (%)	**0 (0.0%)**	**1 (3.0%)**
Urinary incontinence	0 (0.0%)	1 (3.0%)

Incidence was counted by patients with the treatment-related AEs divided by patients exposed to trial medications who had at least one postbaseline measurement.

Number of patients suffered AEs by system organ class was not equal to the sum of patients listed in each AE since some patients experienced multiple AEs in the same category.

[&] Patients were counted twice because patients may suffer more than one AE of a different severity.

Table 4. Quality-of-life evaluation

	PP population		
Characteristic	LEV-ER (n = 29)	LEV-IR (n = 29)	*p*-value
Change from baseline in the QOLIE-31-P score			0.52
Mean ± SD	2.4 ± 10.1	1.5 ± 13.2	
Min-max	(−16.1, 32.7)	(−32.9, 27.2)	
Change from baseline in the Distress score of QOLIE-31-P			0.36
Mean ± SD	−1.0 ± 12.9	2.5 ± 15.5	
Min-max	(−32.1, 21.4)	(−35.7, 42.9)	
Change from baseline in the EQ-5D VAS score			0.03*****
Mean ± SD	7.2 ± 18.9	−1.5 ± 15.3	
Min-max	(−49.0, 50.0)	(−50.0, 20.0)	
VAS score in the EQ-5D at week 12			0.71
Mean ± SD	73.8 ± 14.1	74.6 ± 14.0	
Min-max	(30.0, 100.0)	(50.0, 98.0)	