Efficacy and safety of pregabalin versus levetiracetam as adjunctive therapy in patients with partial seizures: A randomized, double-blind, noninferiority trial

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SUMMARY

Objectives: To assess the comparative efficacy and safety of pregabalin and levetiracetam for the reduction of seizure frequency in patients with partial seizures.

Methods: This was a randomized, double-blind, flexible-dose, parallel-group noninferiority study of pregabalin and levetiracetam (randomized 1:1) as adjunctive treatment in adult patients with refractory partial seizures. The study included a 6-week baseline phase, 4-week dose-escalation phase, and 12-week maintenance phase. The primary endpoint was the proportion of patients with a \( \geq 50\% \) reduction in 28-day seizure rate during the 12-week maintenance phase, as compared with baseline. Noninferiority of pregabalin was declared if the lower limit of the 95% confidence interval (CI) for the difference in responder rates was greater than the prespecified noninferiority margin of \(-12\%\). A key secondary endpoint was the percent change from baseline in 28-day seizure rate during the dose-escalation and maintenance phases.

Results: Five hundred nine patients were randomized to pregabalin (\( n = 254 \)) or levetiracetam (\( n = 255 \)) and 418 (208 pregabalin, 210 levetiracetam) completed the maintenance phase. With both pregabalin and levetiracetam, the proportion of patients with a \( \geq 50\% \) reduction in 28-day seizure rate was 0.59 (difference between groups [95% CI], 0.00 [\(-0.08 \) to 0.09]). Because the lower bound of the 95% CI was greater than the prespecified noninferiority margin of \(-12\%\), pregabalin was not inferior to levetiracetam. There was no significant difference between pregabalin and levetiracetam in the percent change in 28-day seizure rate (median difference [95% CI], 4.1 [\(-2.6 \) to 10.9], \( p = 0.3571 \)). In a post hoc analysis, the proportion of patients who were seizure-free for the maintenance phase was lower with pregabalin (8.4%) than with levetiracetam (16.2%), \( p = 0.0155 \). Safety profiles were similar and consistent with prior trials.

Significance: These results indicate that pregabalin is noninferior, and has a similar tolerability, to levetiracetam as adjunctive therapy in reducing seizure frequency in patients with partial seizures.

KEY WORDS: Seizure, Noninferiority, Clinical trial, Pregabalin, Levetiracetam.

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Epilepsy is typically initiated with a single antiepileptic drug (AED); however, approximately one half of patients do not respond to the first monotherapy and require add-on, adjunctive therapy to control their seizures.\(^1\)\(^2\) While there are a large number of AEDs available,\(^3\)\(^4\) approximately 30% of patients with partial seizures remain resistant to treatment with single or combination AED therapy,\(^5\) although more recent studies suggest that a higher percentage of patients (65–85%) eventually enter long-term remission.\(^6\)

Pregabalin and levetiracetam have both been established as an efficacious adjunctive therapy with favorable
tolerability in patients with partial seizures.\textsuperscript{7–13} Both therapies are approved for adjunctive treatment of partial-onset seizures.\textsuperscript{14–17} In addition, both therapies have proposed mechanisms of action that differ from those of older AEDs, and are less likely to interfere with the pharmacokinetics of other common treatments for partial epilepsy. Pregabalin and levetiracetam have not previously been directly compared in these patients. Moreover, the efficacy of pregabalin and levetiracetam as add-on therapy in patients who remain on treatment (without discontinuing) has not been determined.

Clinical trials should ideally provide both accurate and usable information. Internal validity (accuracy) is usually assessed by showing a difference between two treatments, often with placebo as the comparator. However, determining that a treatment is “better than nothing” may not be clinically informative, and for this reason comparison to another available treatment may be more clinically informative (providing external validity). In patients with partial seizures, a number of AEDs have been shown to be effective as adjunctive therapy in placebo-controlled trials. For these patients and their treating physicians, there have been few controlled head-to-head trials to guide treatment options when seizures persist. New, direct comparisons between well-established, safe, and efficacious treatments can provide needed information on their relative effectiveness and serve to inform treatment decisions in these patients. The inclusion of a placebo as a third arm in such a head-to-head study adds internal validity, but increases the level of study complexity, limits feasibility, and increases risk, and it may be less necessary when both drugs have well-established efficacy within the study population.\textsuperscript{18} For these reasons, such an arm was not included in the present study.

This trial compared the safety and efficacy of pregabalin and levetiracetam as adjunctive therapy to reduce seizure frequency in patients with inadequately controlled partial seizures.

**Figure 1.**
Study design. BID, twice daily.
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**Methods**

**Study design**

This was a randomized, double-blind (DB), flexible-dose, two-arm, parallel-group, noninferiority study conducted in adult patients at 71 centers in Western and Eastern Europe, South and Central America, and Asia between October 2007 and May 2012. The study consisted of a 6-week baseline (screening) phase, a 4-week DB dose-escalation (titration) phase, and a 12-week DB maintenance phase (Fig. 1). Prior trials of levetiracetam and pregabalin in these patients have had similar treatment assessment periods.\textsuperscript{7,9–13} Patients could then enter a blinded continuation phase in which those who had clinical benefit could remain on blinded study medication for a maximum of 2 years or until the last patient completed or discontinued the maintenance phase of the trial (whichever was earlier).

This study commenced prior to the most recent International League Against Epilepsy (ILAE) terminology for the organization of seizures\textsuperscript{19} and, as such, the 1981 terminology\textsuperscript{20} was used to classify seizures. The equivalent 2010 ILAE seizure classification is also noted for each seizure type. The protocol adhered to the Declaration of Helsinki, Good Clinical Practice guidelines, and was approved by each site’s independent ethics committee or independent review board. ClinicalTrials.gov identifier: NCT00537238.

**Patients**

Patients were aged ≥18 years, with a diagnosis of epilepsy with partial seizures (equivalent to focal seizures in the 2010 ILAE classification), which were historically inadequately controlled with at least 2, but no more than 5, prior AEDs. At the time of enrollment, patients were receiving stable dosages of 1 or 2 standard AEDs (other than pregabalin or levetiracetam) and had a minimum of 4 partial seizures with or without secondary generalization during the 6-week baseline phase, with no 28-day period free of partial
seizures. Patients were also required to have had electroencephalography (EEG) and brain computerized tomography (CT) or magnetic resonance imaging (MRI) scan to confirm the absence of a progressive neurologic lesion within the 2 years prior to randomization. In early 2010, in order to standardize the process of defining seizures and ensure consistency in the application of seizure classification across study sites, the Epilepsy Study Consortium Inc. (ESCI) was introduced and reviewed all prior, current, and future patients’ epilepsy history, EEG, brain scan, and seizure descriptions in order to confirm the diagnosis of partial epilepsy and verify seizure classification. Exclusion criteria included evidence of idiopathic generalized epilepsy on the basis of the following: clinical history, description of seizure types, EEG, and review by ESCI. Patients were also excluded if they had seizures caused by an underlying medical illness, absence seizures, Lennox-Gastaut syndrome, status epilepticus in the preceding year, a history of a clinically significant or uncontrolled medical condition that would interfere with study participation (e.g., psychiatric illness, hepatic or renal disease), a history of lack of response to either of the study drugs or hypersensitivity, poor tolerability, or use of gabapentin, pregabalin, or levetiracetam within the preceding 1 month.

**Treatment**

Patients were randomized 1:1 to either pregabalin or levetiracetam using a computer-generated randomization system. Treatment was administered using a DB, double-blind approach with patients receiving either active pregabalin and dummy levetiracetam or active levetiracetam and dummy pregabalin. During the 4-week dose-escalation phase, investigators escalated doses of pregabalin (150, 300, 450, and 600 mg/day) or levetiracetam (1,000, 2,000, and 3,000 mg/day) twice daily, to the highest effective dose (based on clinical criteria whereby patients who continued to experience seizures had their dose titrated up, provided there was acceptable tolerability). Patients started at the minimum dose at week 0 of the study, and dose escalation was permitted at weeks 1, 2, and 4. The patient’s final dose was then continued in the maintenance phase. A one-time dosage reduction of the study drug was permitted during the maintenance phase (for tolerability). Patients were required to maintain their prestudy regimens of other AEDs, with dosage changes not permitted.

**Efficacy endpoints**

The primary and secondary efficacy endpoints were calculated at the end of the 12-week maintenance phase. The primary efficacy endpoint was the responder rate, defined as the proportion of patients who had a $\geq 50\%$ reduction in 28-day seizure frequency (all partial seizures) over the entire 12-week maintenance phase, as compared with baseline. Key secondary efficacy assessments included the percent change in 28-day seizure frequency during the dose-escalation and maintenance phases (i.e., the DB phase) of treatment compared with baseline; the proportion of secondarily generalized tonic–clonic (SGTC) seizure (equivalent to focal seizure evolving to a bilateral, convulsive seizure in the 2010 ILAE classification) responders (defined as those patients who had a reduction in their ratio of SGTC seizures to all partial seizures between the baseline phase and the DB phase); and the proportion of patients seizure-free for the final 28 days of the study. A post hoc analysis of the proportion of patients who were seizure-free over the entire duration of the 12-week maintenance phase was also conducted. Additional secondary endpoints included: the Brief Psychiatric Rating Scale (BPRS),21,22 a composite of 18 items rating severity of psychopathology on a 7-point scale ranging from 1 (not reported) to 7 (severe); the Hospital Anxiety and Depression Scale (HADS),23 two 7-item self-reporting scales (scored from 0–4) measuring anxiety and depression; and the Medical Outcomes Study–Sleep Scale (MOS-SS),24 a set of patient-rated questionnaires assessing sleep quality and quantity, which can be amalgamated into the nine-item overall sleep problems index.

**Assessment methods**

Patients were interviewed at the beginning of the trial, and each seizure type was classified by description. Patients and, when applicable, caregivers were given seizure diaries to record the date and type of any seizures experienced according to the descriptions and categorizes discussed at the beginning of the trial. Seizure frequency was based on entries in the seizure diaries.

Safety and tolerability were assessed by monitoring adverse events (AEs), including clinically significant symptoms and signs, abnormal laboratory test values, changes in physical examination findings, hypersensitivity, and progression/worsening of underlying disease.

**Statistical analyses**

A sample size of 570 randomized patients (400 per-protocol [PP] patients; 200 randomized PP patients per treatment arm) had $>90\%$ power based on the difference in responder rates between treatments, assuming a 45% response for pregabalin and a 40% response for levetiracetam (based on results from prior trials) with a 12% noninferiority margin and $\alpha 0.025$ one-sided test and 95% confidence interval (CI). Noninferiority of pregabalin, compared with levetiracetam, was declared if the lower bound of the one-sided 95% CI for the difference in responder rates between the two treatment groups was greater than the prespecified noninferiority margin of $-12\%$. Although 509 patients were ultimately randomized in the study, this was anticipated to result in a final statistical power for the study ranging from 80% to 90%. This range of power was considered adequate to assess the scientific objectives of the study.

Analysis of the primary endpoint was based on the PP population, which consisted of all randomized patients who
received ≥28 days of study medication during the maintenance phase and had ≥28 days of utilizable seizure diary data during the baseline and maintenance phases with no major protocol violation. Analysis of all other secondary endpoints was based on a modified intent-to-treat population (mITT), defined as all randomized patients who were administered ≥1 dose of study medication, and for whom ≥1 efficacy evaluation was obtained during the baseline phase and during a postbaseline phase. The mITT population was used for all secondary endpoints, which were not noninferiority assessments, in order to include as many patients as possible. The responder rate was also assessed based on the mITT population, to confirm the analysis based on the PP population. Analysis of efficacy endpoints in the PP and mITT populations enabled the determination of the effects of pregabalin and levetiracetam in patients who remained on treatment for the duration of the study. The safety population consisted of all randomized patients who received ≥1 dose of study medication.

Weighted z-score was used to assess the primary endpoint, combining data from pre- and postinterim analyses. Ranked analysis of covariance was used to assess the treatment difference for percent change from baseline in 28-day seizure rate, and Hodges-Lehmann estimation was used to estimate the median difference and 95% CI for percent change from baseline in 28-day seizure rate. Fisher’s exact test was used to assess the last 28-day seizure-free rate. Analysis of variance was used for the analysis of psychometric endpoints such as HADS, MOS-SS, and BPRS.

An unblinded interim analysis of the primary efficacy endpoint was conducted by an external data-monitoring committee (DMC) after approximately 50% of patients had completed the maintenance phase. The DMC recommended that the study continue as planned.

**Results**

**Patients**
A total of 633 patients were screened and 509 randomized to pregabalin (n = 254) or levetiracetam (n = 255). Of these, 208 (81.9%) and 210 (82.4%) completed the 12-week maintenance phase, and 164 (64.6%) and 177 (69.4%) were part of the PP population for pregabalin and levetiracetam, respectively (Fig. 2). Demographic and baseline clinical characteristics were comparable between groups (Table 1). The most common concomitant AEDs during the study were carbamazepine (54.4% of patients), valproic acid (26.3%), topiramate (24.4%), and oxcarbazepine (22.8%).

During the maintenance phase of the study, the median dose of pregabalin was 450 mg/day and of levetiracetam was 2,000 mg/day. The number of patients receiving each dose was distributed across the available doses for both pregabalin (82 [36.2%] at 300 mg/day, 93 [41.1%] at 450 mg/day, and 50 [22.1%] at 600 mg/day [one patient received 150 mg/day]) and levetiracetam (89 [37.9%] at 1,000 mg/day, 85 [36.2%] at 2,000 mg/day, and 61 [26.0%] at 3,000 mg/day).

To ensure consistent application of diagnosis and seizure classification, an independent review by the ESCI was introduced after the start of the study. This included a prospective review of all patients entering the study thereafter and a retrospective review of all patients already enrolled. Upon review, a number of patients who had already entered

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**Figure 2.**

Patient disposition and study populations.

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the study were rediagnosed with generalized seizures (Table 1). These patients were permitted to complete the study but were excluded from the PP population (i.e., the primary analysis).

| Characteristics                                                                 | Pregabalin (N = 254) | Levetiracetam (N = 255) |
|---------------------------------------------------------------------------------|----------------------|-------------------------|
| Sex, n (%)                                                                       | 120 (47.2)           | 125 (49.0)              |
| Male                                                                             | 134 (52.8)           | 130 (51.0)              |
| Female                                                                           |                      |                         |
| Age (years), n (%)                                                               | 213 (83.9)           | 186 (72.9)              |
| 18–44                                                                            | 40 (15.7)            | 67 (26.3)               |
| ≥65                                                                              | 1 (0.4)              | 2 (0.8)                 |
| Age (years), mean ± SD                                                           | 32.7 ± 11.2          | 36.3 ± 12.2             |
| Race, n (%)                                                                      |                      |                         |
| White                                                                            | 103 (40.6)           | 114 (44.7)              |
| Black                                                                            | 4 (1.6)              | 2 (0.8)                 |
| Asian                                                                            | 105 (41.3)           | 87 (34.1)               |
| Other                                                                            | 42 (16.5)            | 52 (20.4)               |
| Weight (kg), mean ± SD                                                           | 67.9 ± 15.8          | 67.5 ± 15.9             |
| Height (cm), mean ± SD                                                           | 165.7 ± 9.9          | 166.0 ± 9.8             |
| Age at diagnosis of epilepsy (years), mean (range)                               | 17.8 (0.0–53.6)      | 19.4 (0.0–74.0)         |
| Years since diagnosis of epilepsy, mean (range)                                 | 15.3 (2.0–52.8)      | 17.3 (1.9–59.6)         |
| Prior AEDs, n (%)                                                                | 22 (8.7)             | 14 (5.5)                |
| 1                                                                                | 162 (63.8)           | 156 (61.2)              |
| 2                                                                                | 42 (16.5)            | 51 (20.0)               |
| 3                                                                                | 17 (6.7)             | 21 (8.2)                |
| ≥5                                                                               | 11 (4.3)             | 13 (5.1)                |
| Concomitant AEDs, n (%)                                                          |                      |                         |
| 0                                                                                | 0                    | 1 (0.4)                 |
| 1                                                                                | 81 (31.9)            | 71 (27.8)               |
| 2                                                                                | 158 (62.2)           | 165 (64.7)              |
| 3                                                                                | 14 (5.5)             | 15 (5.9)                |
| 4                                                                                | 1 (0.4)              | 3 (1.2)                 |
| Seizure history, n (%)                                                           | 0                    | 1 (0.4)                 |
| Partial seizures                                                                 |                      |                         |
| Simple partial                                                                   | 129 (50.8)           | 145 (56.9)              |
| Complex partial                                                                  | 217 (85.4)           | 209 (82.0)              |
| Partial evolving to SGTC                                                        | 171 (67.3)           | 183 (71.8)              |
| Generalized seizures                                                             | 0                    | 1 (0.4)                 |
| Absence                                                                          | 5 (2.0)              | 6 (2.4)                 |
| Unclassified                                                                     | 0                    | 1 (0.4)                 |
| Baseline 28-day seizure frequency (FAS)                                          | 253                  | 254                     |
| n                                                                                | 253                  | 254                     |
| Mean                                                                             | 17.4                 | 16.7                    |
| Median                                                                           | 7.8                  | 7.5                     |
| Baseline 28-day seizure frequency (PP)                                           | 164                  | 177                     |
| n                                                                                | 164                  | 177                     |
| Mean                                                                             | 16.2                 | 13.9                    |
| Median                                                                           | 6.9                  | 6.8                     |

AED, antiepileptic drug; FAS, full analysis set; PP, per-protocol; SD, standard deviation; SGTC, secondarily generalized tonic–clonic.

*No concomitant AED was recorded.
*Patients may have had a history of more than one type of seizure.
*Equivalent to focal without dyscognitive symptoms in the 2010 International League Against Epilepsy (ILAE) classification.
*Equivalent to focal with dyscognitive symptoms in the 2010 ILAE classification.
*Equivalent to focal evolving to a bilateral, convulsive seizure in the 2010 ILAE classification.

The number of patients in the PP population who met the primary efficacy endpoint of a ≥50% reduction in 28-day seizure rate from baseline to the end of maintenance phase.
was 97 (59.1%) in the pregabalin group and 104 (58.8%) in the levetiracetam group (Fig. 3). The lower bound of the 95% CI for the treatment difference between pregabalin and levetiracetam was −8.0%, which was greater than the prespecified noninferiority margin of −12.0%, and thus pregabalin was not inferior to levetiracetam (Fig. 3). The outcome was similar when disabling seizures only (complex partial [equivalent to focal seizures with dyscognitive symptoms in the 2010 ILAE classification] and SGTC seizures) were assessed, with the proportion of patients with a ≥50% reduction in 28-day seizure rate being 67.4% (122 of 181; 95% CI, 60.0–74.2) with pregabalin and 68.3% (99 of 145; 95% CI, 60.7–75.8) with levetiracetam.

An analysis of the responder rate (≥50% reduction in 28-day seizure rate) using the mITT population confirmed the primary analysis and showed a similar response rate (95% CI) between pregabalin (58.0% [51.5–64.4]) and levetiracetam (59.3% [53.1–65.6]) with a treatment difference (95% CI) of −1.4% (−10.3% to 7.6%). As such, the lower bound of the 95% CI for the treatment difference in the mITT population of −10.3% was also greater than the prespecified noninferiority margin of −12%.

There was no significant difference between pregabalin and levetiracetam for the key secondary endpoint of percent change from baseline in 28-day seizure rate during the DB phase, where the median difference (95% CI) was 4.1% (−2.6 to 10.9), p = 0.3571. The proportion of patients who were seizure-free for the final 28 days of the maintenance phase was lower in the pregabalin group (19.9%) than in the levetiracetam group (27.6%), but this difference was not significant (p = 0.0822) (Table 2). In a post hoc analysis, the proportion of patients who were seizure-free for the duration of the maintenance phase was lower with pregabalin (8.4%) than with levetiracetam (16.2%), p = 0.0155.

A post hoc analysis of ≥50% reduction in 28-day seizure rate and being seizure-free for the entire maintenance phase was conducted by treatment dose (Table 3). A ≥50% reduction in seizure rate was more frequent with lower doses of pregabalin (300 and 450 mg/day) and levetiracetam (1,000 mg/day).

The proportion of SGTC responders was similar with pregabalin (41.2%) and levetiracetam (45.5%) (Table 2). In addition, there were no significant differences between pregabalin and levetiracetam on the psychometric measures BPRS, HADS, and MOS-SS (Table 2).

**Safety**

The nature and frequency of treatment-emergent adverse events (TEAEs) were typical of the known AE profile of pregabalin and levetiracetam. From the start of the study through the end of the maintenance phase, there were 188 patients (74.0%) in the pregabalin group and 164 patients (64.3%) in the levetiracetam group with TEAEs (Table 4). The proportions of patients reporting TEAEs were similar for each final dose of pregabalin (74.4% with 300 mg/day, 72.0% with 450 mg/day, and 79.6% with 600 mg/day) and levetiracetam (66.3% with 1,000 mg/day, 64.7% with 2,000 mg/day, and 59.0% with 3,000 mg/day). Types of TEAE and outcomes were also similar for each dose of each treatment.

Somnolence was the most frequent TEAE, occurring in 79 patients (31.1%) with pregabalin and 73 (28.6%) with levetiracetam, followed by dizziness, which was more common with pregabalin, occurring in 56 patients (22.0%), compared with 39 (15.3%) with levetiracetam. Weight increased was more common with pregabalin (9.4%) than levetiracetam (2.0%), whereas nausea was more common with levetiracetam (5.9%) than pregabalin (1.2%). Most TEAEs were mild to moderate in severity. Serious adverse events were reported in 11 patients (4.3%) with pregabalin and 9 (3.5%) with levetiracetam. Sixteen patients (6.3%) in the pregabalin group and 14 (5.5%) in the levetiracetam group discontinued treatment due to a TEAE. There were no clinically significant changes in laboratory test results, EEG recordings, vital signs, or physical examination findings.

**Discussion**

In this randomized, double-blind trial in patients with inadequately controlled partial seizures, pregabalin was...
### Table 2. Secondary efficacy endpoints

| Endpoints | Pregabalin | Levetiracetam | p-Value |
|-----------|------------|---------------|---------|
| Seizure-free for final 28 days<sup>a</sup> | 201 | 210 | 0.0822<sup>b</sup> |
| N | 201 | 210 | |
| Patients, n (%) | 40 (19.9) | 58 (27.6) | |
| 95% CI | 14.4–25.4 | 21.6–33.7 | |
| Seizure-free for maintenance phase<sup>c</sup> | 225 | 234 | 0.0155<sup>b</sup> |
| N | 225 | 234 | |
| Patients, n (%) | 19 (8.4) | 38 (16.2) | |
| 95% CI | 4.8–12.1 | 11.5–21.0 | |
| SGTC responders<sup>d</sup> | 102 | 101 | 0.5724<sup>b</sup> |
| N | 102 | 101 | |
| Patients, n (%) | 42 (41.2) | 46 (45.5) | |
| 95% CI | 31.6–50.7 | 35.8–55.3 | |
| Total BPRS score<sup>e</sup> | 235 | 241 | 0.1697<sup>f</sup> |
| N | 235 | 241 | |
| LS mean change (SE) | −2.70 (0.40) | −1.92 (0.40) | |
| LS mean difference (95% CI) | −0.77 (−1.88–0.33) | | |
| HADS-Anxiety score<sup>f</sup> | 228 | 240 | 0.4008<sup>f</sup> |
| N | 228 | 240 | |
| LS mean change (SE) | −0.89 (0.22) | −1.15 (0.22) | |
| LS mean difference (95% CI) | 0.25 (−0.34 to 0.85) | | |
| HADS-Depression score<sup>f</sup> | 228 | 240 | 0.9749<sup>f</sup> |
| N | 228 | 240 | |
| LS mean change (SE) | −0.46 (0.22) | −0.45 (0.22) | |
| LS mean difference (95% CI) | −0.01 (−0.61 to 0.59) | | |
| MOS-SS sleep index score<sup>h</sup> | 230 | 240 | 0.6344<sup>f</sup> |
| N | 230 | 240 | |
| LS mean change (SE) | −2.69 (0.95) | −3.33 (0.96) | |
| LS mean difference (95% CI) | 0.64 (−2.00 to 3.27) | | |

BPFRS, Brief Psychiatric Rating Scale; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; LS, least squares (LS mean change from baseline to endpoint; LS mean difference is difference between pregabalin and levetiracetam); MOS-SS, Medical Outcomes Study–Sleep Scale; NA, not assessed; SE, standard error; SGTC, secondarily generalized tonic–clonic.

<sup>a</sup>Seizure-free, of all partial seizures, for the final 28 days of the maintenance phase.

<sup>b</sup>p-Value from a two-sided Fisher exact test.

<sup>c</sup>Seizure-free, of all partial seizures, for the entire duration of the 12-week maintenance phase.

<sup>d</sup>A SGTC responder is defined as a patient who shows a reduction from baseline to the double-blind phase (dose-escalation and maintenance phases) in their ratio of 28-day SGTC seizure rate to 28-day all focal seizures rate. Assessed using all patients who recorded ≥1 SGTC during the baseline or dose-escalation and maintenance phases. SGTC seizure is equivalent to focal evolving to a bilateral, convulsive seizure in the 2010 International League Against Epilepsy (ILAE) classification.

<sup>e</sup>Total BPRS score ranging from 18 to 126, with higher scores indicating more impairment.

<sup>f</sup>p-Value from analysis of covariance.

<sup>g</sup>HADS scores ranging from 0 to 21, with higher scores indicating more anxiety or depression.

<sup>h</sup>MOS-SS nine-item sleep problems index scored from 0 to 100, with higher scores indicating more sleep problems.

### Table 3. Patients with a ≥50% reduction in 28-day seizure rate or seizure-free for duration of the maintenance phase by treatment dose (mITT population)

| Endpoints | Pregabalin | Levetiracetam |
|-----------|------------|---------------|
| ≥50% reduction in 28-day seizure rate<sup>a</sup> | 82 | 89 |
| N | 82 | 89 | 61 |
| Patients, n (%) | 53 (64.6) | 63 (70.8) | |
| 95% CI | 54.3–75.0 | 61.3–80.2 | |
| Seizure-free for maintenance phase<sup>b</sup> | 82 | 89 |
| N | 82 | 89 | 61 |
| Patients, n (%) | 9 (11.0) | 23 (25.8) | |
| 95% CI | 4.2–17.7 | 16.7–34.9 | |

CI, confidence interval; mITT, modified intent-to-treat.

<sup>a</sup>Patients with a ≥50% reduction in their 28-day seizure rate from baseline to the end of maintenance phase (mITT population).

<sup>b</sup>Seizure-free, of all partial seizures, for the entire maintenance phase (mITT population).
shown to be noninferior to levetiracetam with respect to the proportion of patients with a ≥50% reduction in their 28-day seizure rate. In addition, there were no significant differences between pregabalin and levetiracetam for any of the secondary efficacy endpoints: change in seizure frequency, proportions of SGTC responders, and seizure-free rate. There were also no differences between pregabalin and levetiracetam in the psychometric and sleep assessments. In a post hoc analysis, there was a difference in the proportion of patients seizure-free for duration of the maintenance phase, with a greater proportion with levetiracetam being seizure-free; however, a longer duration trial would be required to confirm this difference.

It is noted that discontinuations with pregabalin were more likely to occur during the dose-escalation phase whereas, in contrast, discontinuations with levetiracetam were more likely to occur during the maintenance phase (Fig. 2). This difference may reflect the different types of AEs more commonly leading to discontinuation with pregabalin (dizziness and somnolence) and levetiracetam (mood changes) and the time each would take to emerge. Discontinuation rates in this study were 18.1% with pregabalin and 17.6% with levetiracetam, which are within the broad range of those in comparable previous studies of pregabalin (range 17–37%) and levetiracetam (range 4–18%).

To ensure consistency in the application of seizure classification across study sites in this trial, the ESCI was introduced as an independent reviewer of all seizure diagnoses. This review included patient history, seizure description, and an assessment of the consistency in which seizures diaries were completed with regard to seizure type. In total, this assessment identified 54 patients across 15 sites whose retrospective diagnosis indicated that they did not meet the inclusion criteria and were subsequently excluded from the PP population and the primary analysis. However, these patients were included in the mITT population in order to include as many patients as possible in those analyses. The inclusion of an independent review by the ESCI provides confidence that all patients’ diagnoses of partial seizures were accurate and consistent across the study sites.

Although there are a large number of AEDs available, which AED should be selected as adjunctive therapy for patients who do not respond to their initial AED is not always clear. As the majority of new AEDs have been assessed in placebo-controlled trials, comparisons between AEDs are limited to indirect evidence, with direct evidence available only through head-to-head trials. Head-to-head trials of AEDs compare established treatments, often using either a noninferiority design (as required by European regulators) or a superiority design (as required by the U.S. Food and Drug Administration). In this analysis, a noninferiority design was utilized to compare two treatments that are known to be efficacious. As more head-to-head trials are conducted, AEDs can start to be ranked using the criteria in the following order: safety, favorable balance between efficacy and tolerability, pharmacokinetic drug interactions, ease of use, and cost. Ranking can help guide physicians as they make decisions about their patients with inadequate seizure control on current therapy.

Under these criteria, both pregabalin and levetiracetam have shown several advantages over other AEDs. Both have been shown to lack important drug–drug interactions with other AEDs and have a very low potential for idiosyncratic immune-mediated AEs. In a meta-analysis that compared the tolerability profile of pregabalin in randomized controlled trials performed in different patient populations, it was observed that the risk for pregabalin toxicity does not differ across distinct disorders. In fact, toxicity was similar in patients with refractory partial seizures, in whom pregabalin had been added to a previous AED and in patients with other conditions. This is not the case for all AEDs; for example, a similar analysis of lacosamide showed that the risk of toxicity was higher in patients with refractory epilepsies (added to a previous AED) than in patients with other conditions.

When two drugs are combined, there are several possible consequences, where a supra-additive, additive, or infra-additive effect may be observed with respect to both efficacy and tolerability. The best combination would be a supra-additive or additive therapeutic effect and an infra-additive toxicity effect. Speculatively, a combination of two drugs with different mechanisms of action may be more likely to be associated with complementary, and thus, additive or supra-additive, antiepileptic effects with a limited increase in toxicity. This assumption is supported by reports that combinations of two sodium-channel blocking agents (the most common form of AED) are less effective than combinations of drugs with different primary mechanisms of action. In this regard, pregabalin’s mechanism of action is thought to be characterized by binding to the α5δ

Table 4. Treatment-emergent adverse events by treatment group (all causalities)

|                      | Pregabalin (N = 254) | Levetiracetam (N = 255) |
|----------------------|----------------------|-------------------------|
| TEAEs, n             | 557                  | 475                     |
| Patients with TEAEs, n (%) | 188 (74.0)           | 164 (64.3)              |
| Patients with SAEs, n (%) | 11 (4.3)            | 9 (3.5)                 |
| Discontinuations due to TEAEs, n (%) | 16 (6.3)            | 14 (5.5)                |
| Common TEAEs, n (%) | 79 (31.1)            | 73 (28.6)               |
| Somnolence           | 56 (22.0)            | 39 (15.3)               |
| Headache             | 30 (11.8)            | 24 (9.4)                |
| Weight increased     | 24 (9.4)             | 5 (2.0)                 |
| Nasopharyngitis      | 13 (5.1)             | 16 (6.3)                |
| Nausea               | 3 (1.2)              | 15 (5.9)                |

SAEs, serious adverse events; TEAEs, treatment-emergent adverse events. *Occurring in at least 5% of patients in either group.
subunit of voltage-gated calcium ion channels presynaptically, which reduces calcium ion influx with a resultant modulation of excitatory neurotransmitter release, while levetiracetam’s mechanism of action is thought to be through synaptic vesicle protein 2A modulation, which suggests they could combine better with sodium channel blockers and other AEDs than would, for example, two sodium channel blockers together. A pooled analysis of randomized controlled trials of pregabalin supports this suggestion, with the efficacy of pregabalin shown to be consistent regardless of concomitant AEDs.

In this study, the response rate (59% of patients had a ≥50% reduction in their 28-day seizure rate) was higher than in prior studies of pregabalin and levetiracetam (37.3% and 40.1%, respectively, in a pooled analysis), but the reasons for this are unclear. The response rate in this study was based on seizures during the maintenance phase, in contrast to the entire treatment phase in many of the prior studies, which may have partially contributed to this difference. As this study did not include a placebo arm, the impact of the placebo response on the response rate cannot be assessed. A number of features of this trial are associated with a higher placebo response, including that the majority of patients had 1 to 3 prior AEDs (a history of 1–3 AEDs has been associated with a higher placebo response when compared with a history of ≥7 AEDs), and that all patients knew they were receiving active treatment (active-comparator studies have been associated with higher response rates). Significantly, this trial was conducted in Western and Eastern Europe, South and Central America, and Asia, whereas prior studies have typically included patients from only the United States, Canada, and Western Europe. It may be that the placebo response rate is higher, or that patients are more responsive to treatment with pregabalin and levetiracetam, in the rest of the world as compared with the United States, Canada, and Western Europe. It is also possible that the patients in this study represented a milder form of disease, with a relatively shorter history of epilepsy (mean, 15.5 and 17.3 years in this study compared with between 22.8 and 27.7 in prior pregabalin studies), and lower baseline seizure rate (median, 7.5 and 7.8 compared with between 7.3 and 12.3 in prior pregabalin studies).

A number of meta-analyses have concluded that pregabalin and levetiracetam are among the most effective AEDs in patients with refractory partial seizures. The results of this head-to-head noninferiority trial demonstrate that pregabalin and levetiracetam have a similar balance of efficacy and tolerability when used as adjunctive treatment in patients with partial seizures. Pregabalin was shown to be noninferior to levetiracetam for the proportion of patients with a ≥50% reduction in their 28-day seizure rate and there were no significant differences for the secondary efficacy endpoints. Both treatments showed favorable tolerability. These data suggest that pregabalin, together with levetiracetam, should be considered early in the treatment paradigm of adjunctive therapy for patients with partial seizures.

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**Conflict of Interest**

This study was sponsored by Pfizer Inc. Gaetano Zaccara received speaker’s or consultancy fees from the manufacturers of topiramate (Jansen and Cilag); lacosamide and levetiracetam (UCB Pharma); retigabine (GSK); valproic acid (Sanofi-Aventis); and eslicarbazepine and zonisamide (Eisai). Holly Posner, Mary Almas, Lloyd Knapp, and Verne Pitman are employees of Pfizer Inc. 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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