Original article

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Adjunctive lacosamide for focal epilepsy: an open-label trial evaluating the impact of flexible titration and dosing on safety and seizure outcomes

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ABSTRACT – *Aims.* To evaluate the safety and effectiveness of lacosamide in a real-life setting with the use of a flexible dose titration schedule and individualised maintenance doses up to the maximum approved dose of 400 mg/day.

Methods. Adults with a diagnosis of focal seizures, with or without secondary generalization, were enrolled in this open-label Phase IV trial (NCT01235403). Lacosamide was initiated at 100 mg/day (50 mg bid) and uptitrated over a 12-week period to 200, 300 or 400 mg/day, based on safety and seizure control. Although dose increases were to be in increments of 100 mg/day, intermediate doses were permitted at each escalation step for one week for patients known to be particularly sensitive to starting new AEDs. After receiving a stable, effective dose for three weeks, patients entered the 12-week maintenance period. Primary outcomes were incidence of treatment-emergent adverse events (TEAEs) and withdrawal due to TEAEs. Seizure outcomes, all secondary, were median focal seizure frequency, ≥50% reduction in focal seizure frequency, and seizure freedom.

Results. One hundred patients with a mean age of 44 years were enrolled and 74 completed the trial. The incidence of TEAEs was 64.0% (*n*=100), with the most frequently reported (≥5% of patients) being dizziness, headache, and asthenia. Fourteen patients withdrew due to TEAEs, most frequently due to dizziness (six patients; 6.0%), vomiting (two patients; 2%), and tremor (two patients; 2%). Among patients with baseline and maintenance phase seizure data (*n*=75), median reduction in focal seizure frequency from baseline was 69.7% and the ≥50% responder rate was 69.3%. Among 74 patients who completed the maintenance phase, 21 (28.4%) were seizure-free.

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Conclusion. Flexible lacosamide dosing in this open-label trial was associated with a favourable tolerability and safety profile; the nature of the TEAEs was consistent with that observed in previous pivotal trials. Treatment with lacosamide was also associated with effective seizure control.

Key words: focal, seizure, dizziness, flexible dose, a ;tiepileptic, individualised, titration

In clinical trials conducted to determine the efficacy and safety of adjunctive antiepileptic drugs (AEDs), the test drugs are typically administered following forced titration schedules and at fixed doses for a relatively short period of time (Ben-Menachem, 2005). In addition, strict inclusion/exclusion criteria are used to ensure recruitment of a homogeneous patient population. While these and other attributes of randomized controlled trials allow for detection of clear safety and efficacy signals, the applicability of the results to real-life practice, with its diversity of clinical situations and patients, remains limited. Results from Phase IV trials or well conducted observational studies with a more flexible approach can help clinicians determine how AEDs can best be used in a wider population of patients with epilepsy and decide the most appropriate dosing schedules (Mohanraj and Brodie, 2003).

The efficacy and safety of adjunctive lacosamide for the treatment of patients with focal epilepsy have been demonstrated in three pivotal Phase II/III trials (Ben-Menachem *et al*., 2007; Halász *et al*., 2009; Chung *et al*., 2010a). The long-term safety of lacosamide, as well as sustained efficacy, was further demonstrated in open-label extension trials (Husain *et al*., 2012; Rosenfeld *et al*., 2014; Rosenow *et al*., 2015). Results of subsequent prospective, open-label studies have complemented those of the pivotal trials by demonstrating the tolerability of, and effective seizure control with lacosamide among patients in clinical practice (Villanueva *et al*., 2012; Runge *et al*., 2015; Zadeh *et al*., 2015).

In the pivotal trials, based on a forced schedule, lacosamide was titrated over 4-6 weeks from a starting dose of 100 mg/day, with increases of 100 mg/day every week to target doses of 200, 400, or 600 mg/day. A dose-dependent increase in early discontinuation due to adverse events was observed in these trials, with dizziness reported as the most frequent cause of discontinuation. The primary objective of the trial described here was to evaluate the safety and effectiveness of lacosamide under conditions that approximate a real-life setting, particularly with the use of a dose titration schedule that allowed for some flexibility and individualised maintenance doses up to the maximum approved dose of 400 mg/day. Other objectives included characterisation of dizziness and evaluation of differences in safety and seizures outcomes among patients taking traditional sodium channel blocking (SCB) AEDs and those taking AEDs with a different mechanism of action.

Methods

Trial design

This was a Phase IV, multicentre, open-label, interventional trial (SP1007, NCT01235403) conducted at 45 centres across France. The trial protocol, amendments, and patient informed consent were reviewed by national, regional, or independent ethics committees. The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

The trial consisted of a titration phase, which lasted up to 12 weeks, and a 12-week maintenance phase (*figure 1*). Lacosamide was initiated at 100 mg/day (50 mg bid). After 1-3 weeks, as determined by the investigator together with the patient, the dose was increased to 200 mg/day (100 mg bid); the lowest recommended therapeutic dose. After assessment of safety and tolerability at the titration visits, the dose could be further increased to 300 mg/day (150 mg bid) and later to a maximum possible dose of 400 mg/day (200 mg bid). Although dose increases were to be performed in steps of 100 mg/day, intermediate doses, such as 50, 150, 250, or 350 mg/day, at the beginning of each dose escalation step were permitted for patients known to be particularly sensitive to starting new AEDs, but for no longer than one week each.

After receiving a stable, clinically effective dose for three weeks, patients entered the maintenance phase. Only a single change of 100 mg/day within the 200-400-mg/day range was permitted during this 12-week phase. Concomitant AEDs could also be added or withdrawn during the maintenance phase. Patients completing the maintenance phase could continue to receive commercially available lacosamide or had their lacosamide dosage reduced at a recommended rate of 200 mg/week. Patients discontinuing early from the trial also had their lacosamide dosage reduced by 200 mg/week.

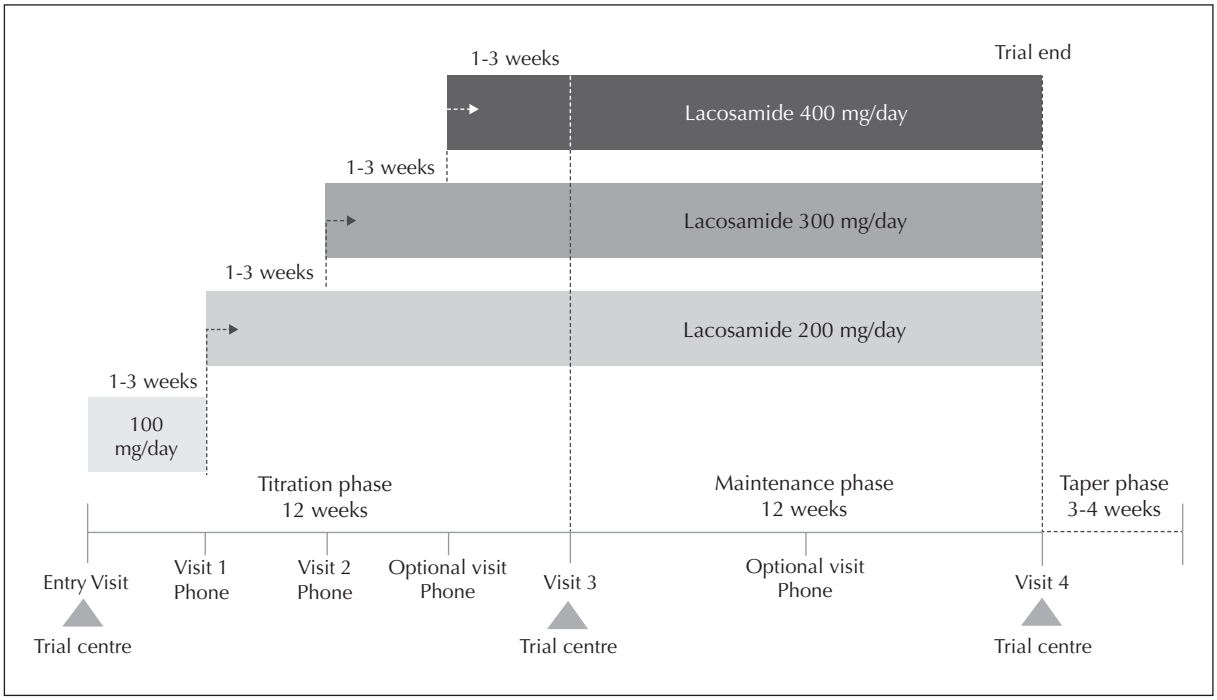

Figure 1. Trial design.

Patient population

Patients 18 years of age or older who had a diagnosis of focal seizures, with or without secondary generalization, were enrolled. Patients had to present with 1-14 seizures per 28 days over the three-month historical baseline period before trial entry, and they were required to be taking 1-3 concomitant AEDs at a stable dose. Vagus nerve stimulation was permitted and counted as a concomitant AED. Patients could not participate in the trial if they experienced focal seizures that were not clearly identifiable or if they had a history of cluster seizures, psychogenic non-epileptic seizures or status epilepticus within 12 months of trial initiation, a progressive neurological disease, or type II or III atrioventricular block. The use of felbamate or vigabatrin was not permitted. Female patients of childbearing age were required to practice contraception for the duration of the trial.

Trial outcomes

There were two primary safety variables: incidence of treatment-emergent adverse events (TEAEs) and withdrawal due to TEAEs. There were no primary efficacy variables, however, several secondary seizure outcomes were included. These were percent change and ≥50% reduction in focal seizure frequency (number of seizures per 28 days) from historical baseline to the end of the 12-week maintenance phase, seizure freedom among patients who completed the 12-week maintenance phase, and retention rate. Retention rate was defined as the percentage of patients who continued to receive lacosamide up to and including Week 24.
An assessment of the characteristics of dizziness was also performed. This included assessment of the frequency, intensity, and timing of onset or worsening of dizziness episodes. The impact of dizziness on daily activities was also evaluated.

Statistical analysis

No formal hypothesis testing was performed during this trial, therefore, data were summarized using descriptive statistics. All analyses were conducted using SAS® (SAS Institute, Cary NC, USA), Version 9.2. The safety set included all patients who received at least one dose of lacosamide during the trial. The full analysis set (FAS) included all patients in the safety set who had a baseline and at least one post-baseline seizure assessment.
A subgroup analysis was performed to evaluate outcomes based on patients' concomitant AED(s). Two subgroups were identified; one consisted of patients with at least one SCB AED in their concomitant AED regimen (which could also include a non-SCB AED) and another of those who were not using any concomitant SCB AEDs. Sodium channel blocking AEDs included carbamazepine, lamotrigine, oxcarbazepine,

rufinamide, eslicarbazepine, and phenytoin medications (phenytoin, phenytoin sodium, ethotoin, fosphenytoin, fosphenytoin sodium, and zentronal).

Results

A total of 100 patients were enrolled in the trial. At six months, 74 had completed the trial and 26 discontinued prematurely. Of the 26 patients who discontinued, 25 did so during titration. The most common reasons for discontinuation were TEAEs (14 patients), withdrawal of consent (four patients), lack of efficacy (two patients), loss to follow-up (two patients), and "other" (four patients). All 100 patients were included in the safety set; of these, 93 patients had post-baseline seizure data and were included in the FAS.

The mean age (±SD) of patients was 44.5 years (±16.2) (*table 1*). The median baseline seizure frequency per 28 days was 3.1 (range: 1-28) and the mean time since diagnosis (±SD) was 20 years (±15.6). Most patients (52.0%) had been exposed to 1-3 lifetime AEDs and were taking at least two concomitant AEDs at baseline (64.0%). The most frequently taken concomitant AEDs were lamotrigine, levetiracetam, and carbamazepine.

The median duration of exposure to lacosamide in the safety set was 169.0 days and the median modal dose during the treatment phase (both titration and maintenance) was 200 mg/day. Modal dose was defined as the daily dose the patients received for the longest duration. For patients who entered the maintenance phase, the mean (±SD) duration of titration to the maintenance dose was 57.9 days (±32.74).

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

Characteristic	*n*=100
Age, mean (± SD) (years)	44.5 (±16.2)
Age range (years)	19-76
Male, *n* (%)	45 (45)
Weight, mean (± SD) (kg)	67.5 (±15.0)
Time since diagnosis[a], mean (±SD) (years)	20.0 (±15.6)
Historical baseline seizures/28 days, median (range)[b]	3.1 (1-28)
Number of lifetime AEDs, *n* (%)	
1-3	52 (52.0)
4-6	21 (21.0)
≥7	9 (9.0)
Unknown	18 (18.0)
Number of concomitant AEDs, *n* (%)	
1	36 (36.0)
2	42 (42.0)
3	22 (22.0)
Most frequently used concomitant AEDs[c], *n* (%)	
Lamotrigine	40 (40.0)
Levetiracetam	26 (26.0)
Carbamazepine	20 (20.0)
Oxcarbazepine	15 (15.0)
Valproate	14 (14.0)
Topiramate	11 (11.0)
Zonisamide	11 (11.0)
Clobazam	10 (10.0)

[a]n=87; [b]n=99, historical baseline defined as the three-month period before trial entry; [c]taken by ≥10% of patients; AED: antiepileptic drug; SD: standard deviation.

Safety outcomes

Overall, 64 of 100 patients (64.0%) experienced at least one TEAE during the trial. Incidence of TEAEs was higher during the titration phase than during the maintenance phase (55.0% *vs* 18.5%). The most frequently reported TEAEs (in ≥5% of patients) throughout the trial were dizziness (42.0%), headache (8.0%), and asthenia (5.0%) (*table 2*). The majority of TEAEs were mild or moderate in intensity; 19 patients reported severe TEAEs, with the most frequent being dizziness (12 patients), convulsion (two patients), and focal seizures with secondary generalization (two patients).

A total of 127 TEAEs reported by 61 patients (61.0%) were considered treatment-related by the investigator; the most frequently reported were dizziness (42.0%), headache (8.0%), and asthenia (5.0%).

Fourteen patients discontinued due to TEAEs. The most frequently reported TEAEs leading to discontinuation were dizziness (6.0%), vomiting (2.0%), and tremor (2.0%). Fourteen patients experienced TEAEs that led to dose reduction; 13 patients in the titration phase and one in the taper phase. The most frequently reported TEAEs that led to dose reduction were dizziness and gait disturbance (nine and three patients, respectively).

Overall, three of 100 patients (3.0%) experienced seven serious AEs (SAEs). One patient reported diplopia, nausea, gait disturbance, and dizziness, all considered treatment-related and resulting in dose reduction. One patient experienced status epilepticus with coma; both events were considered possibly related to treatment. The third patient experienced focal seizures with secondary generalization, which was not considered treatment-related. All SAEs resolved and patients continued treatment.

Overall in the trial, 42 (42.0%) patients reported episodes of dizziness (*table 3*). The majority of these

Table 2. Most commonly reported (by ≥3% of patients) treatment-emergent adverse events according to dose at onset of the TEAE*.

	Dose at onset (mg/day)				
MedDRA Preferred Term, *n* (%)	0-150 (*n*=100)	151-250 (*n*=88)	251-350 (*n*=49)	>350 (*n*=16)	Total (*n*=100)
Dizziness	12 (12.0)	20 (22.7)	9 (18.4)	4 (25.0)	42 (42.0)
Headache	5 (5.0)	1 (1.1)	2 (4.1)	0	8 (8.0)
Asthenia	3 (3.0)	2 (2.3)	0	0	5 (5.0)
Diplopia	3 (3.0)	1 (1.1)	2 (4.1)	0	4 (4.0)
Constipation	4 (4.0)	0	0	0	4 (4.0)
Gait disturbance	2 (2.0)	2 (2.3)	2 (4.1)	0	4 (4.0)
Nausea	1 (1.0)	2 (2.3)	2 (4.1)	0	3 (3.0)
Vomiting	1 (1.0)	0	1 (2.0)	0	3 (3.0)
Vision blurred	2 (2.0)	0	0	1 (6.3)	3 (3.0)
Weight increased	0	1 (1.1)	1 (2.0)	0	3 (3.0)
Complex focal seizure	0	1 (1.1)	1 (2.0)	1 (6.3)	3 (3.0)
Convulsion	1 (1.0)	2 (2.3)	0	0	3 (3.0)
Focal seizure with secondary generalisation	0	1 (1.1)	1 (2.0)	1 (6.3)	3 (3.0)
Somnolence	3 (3.0)	0	0	0	3 (3.0)
Tremor	1 (1.0)	1 (1.1)	1 (2.0)	0	3 (3.0)
Depression	2 (2.0)	1 (1.1)	0	0	3 (3.0)

*Patients could be counted under more than one dose for the same event if the patient had multiple occurrences of the same event while on different doses.

patients reported the episodes to be intermittent, fluctuating in intensity, and with an onset/worsening within four hours of dosing. Most also reported that the episodes had a moderate impact on their daily activities.

The mean (SD) duration of lacosamide treatment at the time of the first onset of dizziness was 46.3 (43.09) days. Patients could have been taking more than one AED at the onset of dizziness.

Safety outcomes were analysed according to patients' concomitant AEDs. Seventy patients had at least one SCB AED among their concomitant AEDs, while 30 patients were not taking SCB AEDs. Sodium channel blocking AEDs used in this trial were lamotrigine (40%), carbamazepine (20%), oxcarbazepine (15%), and phenytoin medications (5%). Among patients taking concomitant SCB AEDs, 64.3% reported TEAEs and 45.7% specifically reported dizziness. Corresponding values among those taking non-SCB AEDs were 64.3% and 33.3%, respectively. Eight patients who discontinued were receiving at least one concomitant SCB AED and six were receiving non-SCB AEDs.

No TEAEs related to hepatotoxicity, suicidality, or cardiac and ECG abnormalities were reported, and physical and neurological examinations did not reveal any clinically relevant findings.

Seizure outcomes

Seizure outcomes were reported for patients in the FAS who had baseline and maintenance phase seizure data (*n*=75). In this group, median reduction in focal seizure frequency (number of seizures/28 days) from baseline to end of maintenance was 69.7% and the ≥50% responder rate was 69.3% (*figure 2*). Among 74 patients who completed the maintenance phase, 21 (28.4%) were seizure-free during the maintenance phase (*figure 2*).

Table 3. Characteristics of dizziness (safety set).

Characteristic, *n* (%)	***n*=100**
Any episode of dizziness	42 (42.0)
≥1 intermittent or fluctuating episode	37 (37.0)
Occurrence (on a daily basis)	
Intermittent	32 (32.0)
Permanent	8 (8.0)
Intermittent and permanent	2 (2.0)
Intensity pattern (on a daily basis)	
Stable	9 (9.0)
Fluctuating	32 (32.0)
Stable and fluctuating	1 (1.0)
Time to onset/worsening after taking lacosamide*	
Within 4 hours	30 (81.1)
>4 hours after	7 (18.9)
At any time	0
Impact on daily activities	
None	2 (2.0)
Moderate	27 (27.0)
Severe	11 (11.0)
Varying	2 (2.0)

*Percentages were calculated using patients in the safety set as the denominator, except for the onset/reinforcement time after lacosamide intake, which was calculated using patients with at least one intermittent or fluctuating episode of dizziness

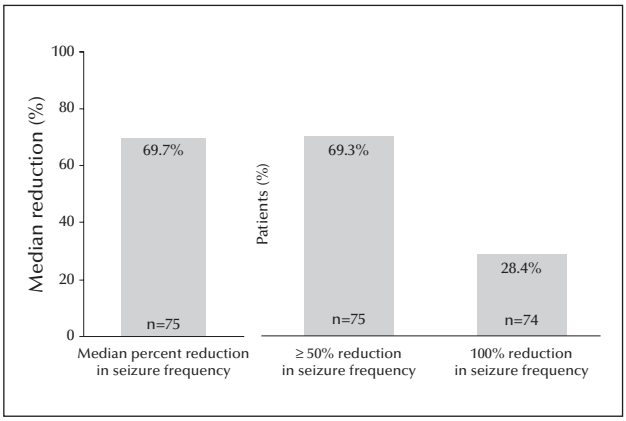

Figure 2. Median percent reduction and proportion of patients experiencing a ≥50% reduction in seizure frequency (seizures/28 days) at the end of the 12-week maintenance phase and proportion of patients who completed the trial and reported no seizures of any type during the maintenance phase.

The retention rate at the end of the maintenance phase (Week 24 of the study) was 73.0%. One additional patient who remained on lacosamide through the maintenance period was excluded from this analysis following transition to commercial lacosamide just before completing maintenance.

In the subgroup analysis, based on concomitant AED use, 72.5% (42/58) of patients receiving SCB AEDs and 58.8% (10/17) of patients receiving non-SCB AEDs had a ≥50% reduction in seizure frequency. The retention rate was 80.0% (56/70) for patients in the SCB AED group and 56.7% (17/30) for those in the non-SCB AED group.

Discussion

The three lacosamide pivotal trials were randomized, double-blind, placebo-controlled trials with a similar design; patients entered a 4- or 6-week forced titration period to a predefined target dose, followed by a 12-week maintenance period (Chung *et al*., 2010b). All concomitant AEDs also had to be maintained at stable doses. In the current open-label trial, the safety and effectiveness of lacosamide was evaluated using a dose titration schedule that allowed for some flexibility, and individualised maintenance doses; the 100-mg dose titration steps took place over a period of 1-3 weeks rather than a set one-week period, and during the 12-week maintenance phase, a single change of 100 mg/day within the 200-400-mg/day range was permitted, as well as addition or withdrawal of concomitant AEDs. Given the flexibility in the titration schedule and maintenance dosing, which allowed better treatment individualization within the limits of the protocol, as well as flexibility in the use of concomitant AEDs, the trial closely resembled real-life clinical practice.

The overall incidence of TEAEs during treatment (titration and maintenance) was 64.0%, with a higher incidence during titration than during maintenance (55.0% *vs* 18.7%). Fourteen (14%) patients discontinued due to TEAEs, most frequently dizziness, vomiting, and tremor.

Given the known safety profile of lacosamide, dizziness was expected to be one of the most frequently reported AEs in the current trial. Consequently, dizziness was assessed specifically by asking participants questions about the frequency, intensity, and timing of the onset of dizziness in relation to taking lacosamide. Indeed, dizziness was the most frequently reported AE in the trial with an incidence of 42%. The next most common AEs were headache (8.0%) and asthenia (5.0%). Patients who experienced dizziness described the episodes as intermittent, fluctuating in intensity, with an onset or worsening within four hours of dosing. With this knowledge, patients could be advised to be aware of the timing of the onset of dizziness after taking their medication. This way, they could adapt their activities as much as possible to minimize the impact of dizziness. Most patients (27/42) reported that dizziness had a moderate impact on their

daily activities, while 11 reported that the impact was severe. While the greater scrutiny of dizziness provided some further insight into this particular AE, it may also explain its notably high incidence relative to the pivotal trials; in the current trial, the incidence of dizziness was 42.0% with median modal lacosamide dose of 200 mg/day, while in the pivotal trials it was 30.6% among patients taking 200-600 mg/day. In fact, directing physicians to ask specific questions on dizziness may have led to greater reporting of this AE than would have otherwise been reported if not questioned. This observation can be described as a nocebo effect, the phenomenon whereby negative expectations can lead to adverse outcomes, or in other words, individuals who are aware they might experience a certain side effect are more likely to experience it (Faasse and Petrie 2013; Tan *et al*., 2014).

As well as general safety, several additional TEAEs were given special consideration; these were hepatotoxicity, suicidality, and cardiac and ECG abnormalities. No TEAEs related to these terms were reported.

There was no primary efficacy outcome in this trial, but several secondary outcomes were included to evaluate the impact of treatment with lacosamide on seizure frequency. Among patients who entered the maintenance phase, the median reduction in focal seizure frequency from baseline to the end of the maintenance was 69.7% and the 50% responder rate was 69.3%. Among those who completed the maintenance phase, 28.4% were seizure-free. Results for the three aforementioned seizure outcomes were higher than those reported in the pivotal trials. In the analysis of data pooled from the pivotal trials, the median reduction in seizure frequency was 33.3% and 36.8% in the lacosamide 200 and 400-mg/day treatment groups, respectively (Chung *et al*., 2010b). Corresponding values were 34.1% and 39.7% for the 50% responder rate, and 2.7% and 3.3% for the seizure freedom rate, respectively. The greater response rates observed in the current trial are likely due to its open-label design and to the inclusion of patients with less treatment-refractory epilepsy. Notably, they were taking fewer concomitant AEDs, they had taken fewer lifetime AEDs, and their seizure frequency at trial entry was lower compared with patients in the pivotal trials. Additionally, seizure outcomes in the current trial are presented only for those patients who completed titration and entered maintenance.

A subgroup analysis was conducted to compare outcomes based on the mechanism of action of concomitant AEDs. Results of a post hoc analysis of data from the pivotal trials had shown that there were fewer discontinuations due to TEAEs among patients who did not have a SCB AED in their treatment regimen compared with those who did (Saké *et al*., 2010). As noted by the authors, the observation that discontinuations due to TEAEs were not dose-dependent when lacosamide was added to non-SCB AEDs suggested a potential for improved tolerability, especially at higher lacosamide doses (Saké *et al*., 2010). There was also a trend toward greater efficacy among patients not taking SCB AEDs, again at higher lacosamide doses (Saké *et al*., 2010). Results of the subgroup analysis in this trial did not follow these trends; in contrast, the safety profile of lacosamide was similar in both subgroups and the 50% responder rate was numerically greater among patients taking a concomitant SCB AED rather than those taking only concomitant non-SCB AEDs (72.5% *vs* 58.8%). Similarly, the retention rate was higher among patients taking a concomitant SCB AED compared with those who were not (80.0% *vs* 57.0%).

Results from observational studies that have also included analyses based on the mechanism of action of concomitant AEDs are inconsistent. In one of the first prospective, observational studies of lacosamide, the Spanish RELACOVA study, both safety and seizure outcomes were better among patients not taking SCB AEDs (Villanueva *et al*., 2012). In another relatively large-scale, prospective, observational study, there was a significantly greater incidence of TEAEs in the group of patients taking concomitant SCB AEDs compared with the group that were not, but seizure outcomes did not vary between the two groups (Kamel *et al*., 2013). In a five-year audit by the Glasgow group, outcomes were reported to be similar for both groups of patients, and after having reached the study endpoint, the proportion of patients remaining on lacosamide and a SCB AED or an AED with another mechanism was identical at 76% (Stephen *et al*., 2014). The investigators concluded that in some patients, with dose manipulation, SCB AEDs could be combined with lacosamide as successfully as AEDs with other mechanisms of action (Stephen *et al*., 2014). Finally, in the German VITOBA study, similar to the Glasgow audit, no differences in safety or seizure outcomes were observed between the two groups (Runge *et al*., 2015). The advantages of the VITOBA study were the large number patients (269 patients were taking concomitant SCB AEDs and 313 patients were taking non-SCB AEDs) and that most patients were only on a single concomitant AED.

Results of the subgroup analysis in the current trial suggest that flexibility in the titration schedule and dosing of adjunctive lacosamide could lead to improved effectiveness for patients taking SCB AEDs. However, these findings should be interpreted with caution, as they are limited by confounding factors, the most important of which is that patients in the SCB AED group could be taking both SCB and non-SCB AEDs. Other

confounding factors include the use of multiple concomitant AEDs by some patients, the smaller number of patients taking non-SCB AEDs only (30.0% *vs* 70.0%), and the possibility of adjusting the dose of concomitant AEDs during the trial.

Overall, results of this open-label trial, conducted to resemble a real-life setting, showed that treatment with adjunctive lacosamide was associated with effective seizure control and favourable tolerability, as indicated by the 73.0% retention rate. While both seizure and safety outcomes appeared improved relative to the pivotal trials, a direct comparison of the results from the current trial with those of the pivotal trials cannot be made. In addition to the differences in the patient populations mentioned above, in the pivotal trials, some patients received lacosamide doses of 600 mg/day, which is associated with a higher incidence of adverse events. Nonetheless, in the current trial, the incidence of TEAEs was 64.0% among patients taking lacosamide at 200-400 mg/day, while in the pivotal trials, the incidence of TEAEs was 69.6% and 82.2% in the 200 and 400-mg/day groups, respectively. The nature of the TEAEs was generally consistent with that observed in the pivotal trials.

Since initiation of this trial, a number of prospective observational studies have been completed, which together provide detailed insight into how lacosamide is used in a real-life setting. The aforementioned RELACOVA study included 158 patients (Villanueva *et al*., 2012). The retention rate was 81.0% and 69.6% at 6 and 12 months, respectively, with mean±SD lacosamide dosages of 314.1±93.7 mg/day and 324.5±108.1 mg/day, respectively. Seizure freedom at 12 months was 24.1%. The incidence of TEAEs was 49.4% over a 12-month period, with most AEs occurring during the first three months of treatment. The Glasgow audit included 160 patients, with 21.9% reporting seizure freedom at six months on a median lacosamide dosage of 100 mg/day (range: 50-500 mg/day) (Stephen *et al*., 2014). Adverse events led to discontinuation in 15% of patients, most frequently due to nausea and vomiting, dizziness, sedation, headaches, tremor, and ataxia. In an Australian study of 128 patients, 11% were seizure-free over an average period of 35 weeks, and the mean lacosamide dosage was 250 mg/day (Kamel *et al*., 2013). The incidence of TEAEs in the overall population was 41%. In these studies, as in the current trial conducted in France, improved seizure outcomes were obtained with lower doses, and the tolerability profile of lacosamide was better relative to the pivotal trials. These observations are also similar to those made in studies with other AEDs, including zonisamide (Dupont *et al*., 2010), topiramate (Krakow *et al*., 2007), and levetiracetam (Morrell *et al*., 2003; Steinhoff *et al*., 2007), and indicate that flexible dosing may lead to improved tolerability.

In conclusion, results of this trial can help physicians adjust the dose of lacosamide based on their patients' tolerability of, and response to lacosamide. Insights into the frequency, intensity, and timing of the onset of dizziness in relation to taking lacosamide can also help patients minimise the impact of this adverse event on their daily activities.

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) List the main differences between this open-label trial and the pivotal lacosamide trials and describe how such a trial can further improve our understanding of lacosamide's role in the treatment of patients with epilepsy

(2) As an adverse event, dizziness was evaluated in detail in this lacosamide trial. What were the main findings of the analyses?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".