Acta Neurologica Scandinavica

Acta Neurol Scand 2016: 133: 136–144 DOI: 10.1111/ane.12451

ACTA NEUROLOGICA
SCANDINAVICA

Long-term adjunctive lacosamide treatment in patients with partial-onset seizures

Rosenow F, Kelemen A, Ben-Menachem E, McShea C, Isojarvi J, Doty P, on behalf of the SP774 study investigators. Long-term adjunctive lacosamide treatment in patients with partial-onset seizures. Acta Neurol Scand 2016: 133: 136–144.
© 2015 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Objective – To evaluate long-term (up to 5.5 years) safety, seizure reduction, and maintenance of efficacy of the antiepileptic drug (AED) lacosamide as adjunctive treatment in an open-label extension trial (SP774; ClinicalTrials.gov: NCT00515619). *Methods* – Three hundred and seventy-six adults with partial-onset seizures taking 1–3 AEDs enrolled following completion of a double-blind trial of adjunctive lacosamide. During open-label treatment, dosage of lacosamide (100–800 mg/day) and/or concomitant AEDs could be adjusted to optimize tolerability and seizure control. *Results* – Kaplan–Meier estimates of patient retention were 74.5% at 12 months, 52.9% at 36 months, and 40.6% at 60 months; median open-label treatment duration was 1183 days (~3.2 years). The most frequently reported treatment-emergent adverse events were dizziness (24.2%), headache (14.4%), diplopia (13.8%), and nasopharyngitis (13.8%); 9.0% of patients discontinued due to adverse events, most commonly dizziness (1.3%). Median percent reduction in 28-day seizure frequency from baseline of the double-blind trial was 49.9% overall, 55.4% for 1-year completers, and 62.3% for 3-year completers. Overall, 50.0% of patients were considered ≥50% responders (achieved ≥50% reduction in 28-day seizure frequency); 55.9% of 1-year completers and 63.0% of 3-year completers were ≥50% responders. *Conclusion* – In eligible patients who entered the open-label extension trial, lacosamide was generally well tolerated. For most patients within each yearly completer cohort, seizure reduction was maintained over time.

F. Rosenow[1], A. Kelemen[2], E. Ben-Menachem[3], C. McShea[4], J. Isojarvi[4,*], P. Doty[4], on behalf of the SP774 study investigators**

[1]Epilepsy Center Frankfurt Rhine-Main, Center of Neurology and Neurosurgery, Goethe University, Frankfurt a. M., Germany; [2]National Institute of Neurosciences, Budapest, Hungary; [3]Institute of Clinical Neurosciences, Division of Neurology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [4]UCB Pharma, Raleigh, NC, USA

Key words: lacosamide; open label; partial-onset seizures; responders; safety; tolerability

F. Rosenow, Epilepsy Center Frankfurt Rhine-Main, Center of Neurology and Neurosurgery, Universitätsklinikum, Goethe University, Schleusenweg 2-16, 60528 Frankfurt a. M., Germany
Tel.: +49 69 6301 7466
Fax: +49 69 6301 84466
e-mail: rosenow@med.uni-frankfurt.de

*Present address: Lundbeck, Deerfield, IL USA:

**See Appendix for the SP774 study investigators.

Accepted for publication May 26, 2015

Introduction

Lacosamide is an antiepileptic drug (AED) approved as monotherapy or adjunctive therapy in adults with partial-onset seizures (POS) in the USA (1) and as adjunctive therapy in adults with POS in the European Union (2). The lacosamide clinical development program included three pivotal double-blind, placebo-controlled trials evaluating adjunctive treatment up to 600 mg/day (3–5). The first trial showed the efficacy of lacosamide in reducing 28-day seizure frequency in patients with POS uncontrolled by one or two AEDs (3). Two further trials, one in the USA (5) and one in Australia and Europe (4), confirmed the efficacy of lacosamide as adjunctive treatment in reducing the frequency of POS in an expanded population of patients taking up to three AEDs. The US trial confirmed that lacosamide was efficacious at dosages of 400 and 600 mg/day, but with a more favorable safety profile provided by the 400 mg/day dosage under the forced-titration design; the European/Australian trial established the efficacy and tolerability of both 200 and 400 mg/day lacosamide.

Given the chronic course of epilepsy and the likely need for extended treatment, long-term safety data for any AED are clinically valuable to rule out an increase in adverse event (AE) frequency or severity over time and to identify

potential new AEs associated with prolonged treatment. Long-term safety and efficacy of lacosamide has been evaluated in two open-label extensions (OLE), following patients from Phase II trials (6) and from the US Phase III double-blind trial (7). These studies showed that lacosamide was well-tolerated for up to 8 years as adjunctive treatment at dosages up to 800 mg/day and suggested long-term reduction in seizure frequency. The current paper reports results from an OLE trial that followed patients from the Phase III trial conducted in Europe and Australia for up to 5.5 years.

Methods

Trial design

This Phase III OLE trial (SP774; ClinicalTrials.gov: NCT00515619) was conducted between December 2004 and August 2010 at 71 sites in Europe and Australia. Approval was obtained from an Independent Ethics Committee, as defined by local regulations, and in compliance with Good Clinical Practice guidelines and the International Conference on Harmonization. All patients provided written informed consent before participating.

Participants

Patients could opt to enter the OLE if they were willing and able to comply with study requirements and had completed the maintenance and transition phases of the randomized double-blind trial SP755 (4) and, in the opinion of the investigator, were expected to benefit from continued participation. Patients were excluded from entry to the OLE if they were receiving other investigational drugs, met withdrawal criteria from the previous trial, or were experiencing an ongoing serious AE.

In the double-blind trial (4), 485 patients, 16–70 years of age, with a diagnosis of POS with or without secondary generalization (ILAE, 1981), were randomized across three treatment arms to lacosamide 400 mg/day, 200 mg/day, or placebo. These patients were required to have had POS for ≥2 years despite prior therapy with at least two AEDs, and entered the trial on a stable dosage regimen of 1-3 AEDs, with or without vagus nerve stimulation. On average, patients were to have ≥4 POS per 28 days during the 8-week period before enrollment to the double-blind trial and during the 8-week baseline period. Seizure-related exclusion criteria for the trial included psychogenic seizures, seizure clustering during the 8-week period before trial entry or during the baseline period, history of primary generalized seizures, history of status epilepticus in the 12 months before trial entry, and concomitant or previous felbamate or vigabatrin therapy in the 6 months before trial entry.

Treatment

Following completion of the maintenance phase of the double-blind trial, patients underwent a blinded 2-week transition phase during which they were titrated to or maintained at a lacosamide dosage of 200 mg/day for entry to the OLE. Lacosamide was administered as oral tablets taken in two daily doses (morning and evening). To attain optimal tolerability and seizure control during the OLE, lacosamide dosage could be increased/decreased at the investigator's discretion (100 mg/day per week within 100–800 mg/day range), and dosage of concomitant AEDs could be increased/decreased, or tapered and discontinued to achieve lacosamide monotherapy. Commercially available AEDs could be introduced only when a patient had not responded optimally to a maximum tolerated dosage of lacosamide.

Outcomes

Clinic visits were scheduled monthly for the first 2 months, every 2 months for the remainder of the first year, every 4.5 months during the second year, and every 6 months thereafter. Primary variables included incidence of AEs and serious AEs, and discontinuation due to AEs. Treatment-emergent AEs (TEAEs) were defined as events starting or worsening on or after first lacosamide dose in the OLE and within 30 days following the final dose of lacosamide. Other safety variables were changes from double-blind baseline in ECGs, vital signs, body weight, and clinical laboratory parameters (all assessed at each clinic visit).

Efficacy was evaluated by changes in 28-day seizure frequency and responder rates (percentage of patients achieving a ≥50% or ≥75% reduction in 28-day seizure frequency relative to baseline of the double-blind trial) among yearly completer cohorts during open-label treatment. Seizure freedom was assessed during the OLE using the subset of patients who reported the respective seizure types in the double-blind baseline period and during the double-blind trial. *Post hoc* assessments of seizure freedom included maximum duration of

continuous seizure freedom, percentage of patients free from any seizure type within completer cohorts, and percentage of patients free from secondarily generalized seizures (SGS) within completer cohorts.

Analyses

Descriptive statistics were used to summarize safety and efficacy results and were calculated using SAS® version 9.1 or higher (SAS Institute Inc., Cary, NC, USA). Assessments of efficacy were based on seizure diary data and were presented for the open-label treatment period or by time interval. For all safety and efficacy analyses, only reported data were used in each analysis time interval.

The safety set (SS) included all patients who received at least one dose of lacosamide during the OLE. The full analysis set (FAS) included patients in the SS who had data available for at least one post-baseline seizure diary day. Yearly completer cohorts comprised patients in the FAS who were exposed to lacosamide and had available seizure diary data for the duration of the specified interval. For example, a 1-year completer cohort comprised patients treated with lacosamide for at least 1 year (where 1 year was defined as 12 months of 28 days) who also had available seizure diary data for 1 year.

Exposure to lacosamide was assessed using modal dosage, defined as the lacosamide dosage received for the longest duration for each patient, presented in 100 mg/day increments. Patient retention rates were estimated using Kaplan–Meier methods.

Results

Trial population

Of the 399 patients completing the SP755 double-blind trial (4), 376 (94%) enrolled in the OLE, all of whom received ≥1 dose of open-label lacosamide and had seizure diary data (included in both the SS and the FAS). The most common concomitant AEDs taken during the OLE included carbamazepine (47.6%), valproate (36.2%), topiramate (32.2%), lamotrigine (31.6%), levetiracetam (23.4%), and oxcarbazepine (16.5%). Of the 160 (42.6%) patients who completed the OLE, 136 (85.0%) continued taking commercially available lacosamide. The main reasons for discontinuation were lack of efficacy (24.5%), withdrawn consent (17.6%), and AEs (9.0%; Table 1).

Table 1 SP774 baseline characteristics and disposition

Characteristics (SS)	$N = 376$
Age at trial entry, mean years (SD)	37.8 (11.5)
Gender, no. (%) male	207 (55.1)
Ethnic origin, no. (%) Caucasian	375 (99.7)
BMI, mean kg/m^2 (SD)	25.8 (5.0)
Time since diagnosis, mean years (SD)[a]	22.2 (12.4)
Seizure frequency per 28 days, median (min, max)[a]	10.5 (3.5, 2416)
Maximum duration of continuous seizure freedom, median (min, max), days[a]	8.0 (0.0, 32.0)
Seizure classification, no. (%)[a]	
Simple partial seizures	139 (37.0)
Complex partial seizures	335 (89.1)
Secondarily generalized seizures	295 (78.5)
Lifetime AED use, no. (%)[a]	
1–3	113 (30.1)
4–6	123 (32.7)
≥7	137 (36.4)
Number of concomitant AEDs, n (%)[a]	
1	47 (12.5)
2	185 (49.2)
3	144 (38.3)
Active vagus nerve stimulation, no. (%)[a]	28 (7.4)

Disposition (SS)	*n* (%)
Treated	376 (100)
Completed	160 (42.6)
Continued to commercial lacosamide[b]	136 (85.0)
Tapered off lacosamide[b]	24 (15.0)
Discontinued	216 (57.4)
Reasons for discontinuation:	
Lack of efficacy	92 (24.5)
Withdrawn consent	66 (17.6)
Adverse event	34 (9.0)
Unsatisfactory compliance	6 (1.6)
Lost to follow-up	4 (1.1)
Protocol deviation	3 (0.8)
Other[c]	11 (2.9)

[a]Data reported from baseline of the double-blind trial.
[b]Percentages for patients who continued to commercial lacosamide or tapered off lacosamide are based on the number of patients who completed the trial.
[c]It includes two patients who discontinued when lacosamide became commercially available.

Lacosamide exposure

Kaplan–Meier estimated retention rates were 74.5% at 12 months, 61.4% at 24 months, 52.9% at 36 months, 47.6% at 48 months, and 40.6% at 60 months (Fig. 1). Median treatment duration was 1183 days (~3.2 years) with 1005.7 patient-years of exposure. Median modal dosage of lacosamide was 400 mg/day; 219 patients (58.2%) had a modal dosage of 400 mg/day or higher (Fig. 2).

Of 280 patients who received lacosamide for ≥1 year, 8 (2.9%) were on lacosamide monotherapy for ≥1 year. The modal dosage during the open-label treatment period for these patients on lacosamide monotherapy was >600 mg/day ($n = 1$), 600 mg/day ($n = 5$), and 400 mg/day

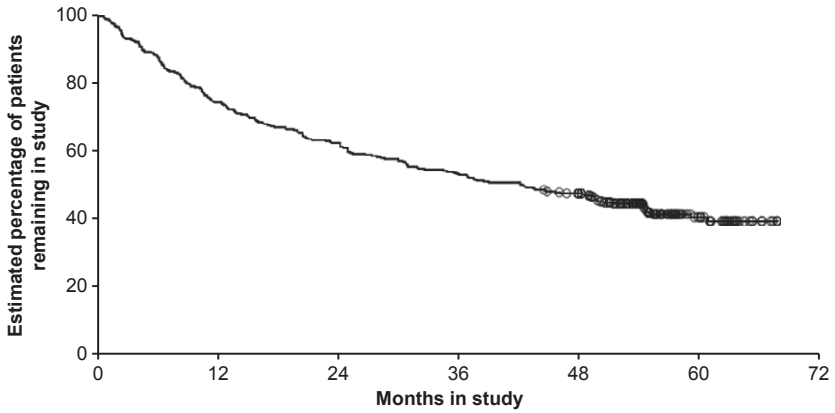

Figure 1. Estimated patient retention on lacosamide treatment during open-label treatment period: Kaplan–Meier analysis (N = 376) (All patients had an opportunity to complete approximately 40 months of open-label lacosamide treatment. Patients who did not prematurely discontinue were censored on the date of the last lacosamide dose; 'o' represents ≥1 censored event.).

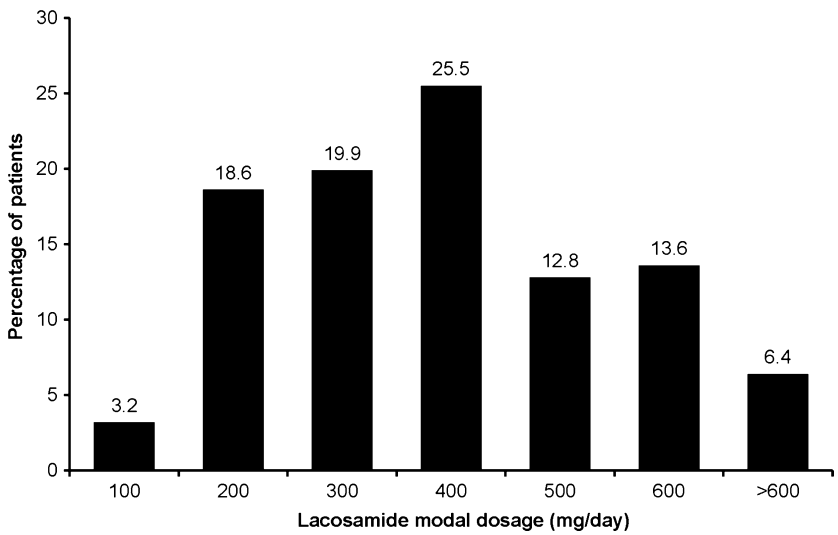

Figure 2. Lacosamide exposure during open-label treatment period by modal dosage

(n = 2). No particular pattern in the seizure types during baseline was observed among these patients.

Safety

During open-label treatment, 311 (82.7%) patients reported ≥1 TEAE, most frequently dizziness (24.2%), headache (14.4%), diplopia (13.8%), and nasopharyngitis (13.8%; Table 2). Most TEAEs were mild or moderate in intensity; of the 311 patients with TEAEs, 254 (81.7%) experienced TEAEs with a maximum intensity of mild or moderate. Of 33 (8.8%) patients who experienced TEAEs that led to discontinuation, only dizziness led to discontinuation in ≥1% of patients [5 patients (1.3%)].

A number of TEAEs that were reported with a low incidence are of particular relevance to

Table 2 Incidence of most common treatment-emergent adverse events (reported by ≥5% of patients)

Adverse event[a]	No. (%) patients[b] (N = 376)
Dizziness	91 (24.2)
Headache	54 (14.4)
Diplopia	52 (13.8)
Nasopharyngitis	52 (13.8)
Convulsion	32 (8.5)
Vertigo	31 (8.2)
Back pain	28 (7.4)
Somnolence	28 (7.4)
Vomiting	25 (6.6)
Tremor	23 (6.1)
Fatigue	22 (5.9)
Contusion	21 (5.6)
Depression	20 (5.3)
Balance disorder	19 (5.1)

[a]Medical Dictionary for Regulatory Activities (MedDRA) preferred term.
[b]Patients experiencing events that started on or after the first dose of lacosamide in the OLE (ongoing AEs from SP755 were not considered treatment emergent).

patients with POS. Memory impairment was reported by 13 patients (3.5%), cognitive disorder by 10 patients (2.7%), and amnesia by two patients (0.5%). One patient each discontinued for TEAEs of memory impairment and cognitive disorder. TEAEs related to suicide (suicidal ideation or suicide attempt) were reported by four patients (1.1%), two of which were rated as serious and resulted in discontinuation. Weight increased was reported as a TEAE in seven patients (1.9%); weight decreased was reported as a TEAE in 12 patients (3.2%), two (0.5%) of whom discontinued due to this TEAE. Fourteen patients (3.7%) reported rash and one patient reported pruritic rash; of the 15 TEAEs related to rash, one event was classified as serious and none led to trial discontinuation.

The most common cardiac- or ECG-related TEAE was chest pain reported in nine patients (2.4%) (this preferred term does not differentiate between cardiac and non-cardiac origin), two of which were serious and none led to trial discontinuation. Four patients (1.1%) discontinued from the trial due to five TEAEs related to cardiac or ECG abnormalities; four were serious (ischemia and tachycardia in one patient, ECG QT-corrected interval prolonged, and acute myocardial infarction) and one was not (ECG QT-corrected interval prolonged). Three patients (0.8%) experienced TEAEs of syncope; none was a serious TEAE or led to discontinuation from the trial.

Eighty-seven patients (23.1%) experienced a total of 149 serious TEAEs. Three serious TEAEs occurred with an incidence ≥1%: convulsion (4.0%), epilepsy (1.9%), and status epilepticus (1.3%). Serious TEAEs considered by the investigator to be related to lacosamide occurred in 24 patients; only convulsion (five patients) and coordination abnormal (two patients) were reported with more than a single occurrence. Three patients died during the trial as a result of the following serious TEAEs: status epilepticus, subarachnoid hemorrhage, and intracranial pressure increased in a single patient; cerebral hemorrhage; and brain neoplasm malignant. All of the deaths were considered not related or unlikely to be related to trial medication by the investigator.

No clinically relevant changes in hematology, clinical chemistry, vital signs, and body weight were associated with long-term lacosamide. A review of ECG data showed that long-term lacosamide was not associated with a change in heart rate or with a prolongation of the QTc interval. Compared with the double-blind trial baseline (157.5 ± 20.8 ms), there was a small increase in PR interval (mean increase at Week 168: 8.4 ± 14.5 ms); five patients (1.4%) had a QRS duration >140 ms. The magnitude of these changes generally did not change with increasing duration of lacosamide exposure.

Efficacy

Seizure frequency and responder rates – Median percent reduction in 28-day seizure frequency from double-blind baseline for the entire open-label treatment period was 49.9%, and by 6-month time intervals of lacosamide exposure were 45.9% (>0–6 months), 55.2% (>6–12 months), 63.0% (>12–18 months), 61.6% (>18–24 months), 65.3% (>24–36 months), and 67.9% (>36–48 months). By yearly completer cohorts, median percent reductions in seizure frequency during the overall open-label treatment period were 55.4% (1-year completers), 62.3% (3-year completers), and 77.9% (5-year completers). Within each completer cohort, median percent reduction from double-blind baseline in seizure frequency was sustained over time (Fig. 3).

Over the entire open-label treatment period, ≥50% responder rate was 50.0% and ≥75% responder rate was 23.7%. By 6-month time intervals of lacosamide exposure, ≥50% responder rates were 45.7% (>0–6 months), 54.4% (>6–12 months), 64.9% (>12–18 months), 65.3% (>18–24 months), 65.1% (>24–36 months), and 62.8% (>36–48 months). Overall, 55.9%, 63.0%, and 75.0% of patients in the 1-year, 3-year, and 5-year completer cohorts were ≥50% responders, with a similar trend observed for the ≥75% responder rate. Within all yearly completer cohorts, the ≥50% and ≥75% responder rates were sustained over time (Fig. 4).

Seizure-free status and percentage of seizure-free days – In the *post hoc* analysis evaluating seizure freedom by completer cohort, 24.4% (68/279) of 1-year completers, 30.0% (60/200) of 3-year completers, and 50.0% (18/36) of 5-year completers were seizure free for ≥6 months. The median longest duration of continuous seizure freedom during the open-label treatment period was 49.0 days for 1-year completers, 64.0 days for 3-year completers, and 158.5 days for 5-year completers.

For patients with SGS at double-blind baseline and during the double-blind trial, freedom from SGS for ≥6 months during open-label treatment was observed in 45.4% (44/97) of 1-year completers, 53.5% (38/71) of 3-year completers, and 52.6% (10/19) of 5-year completers.

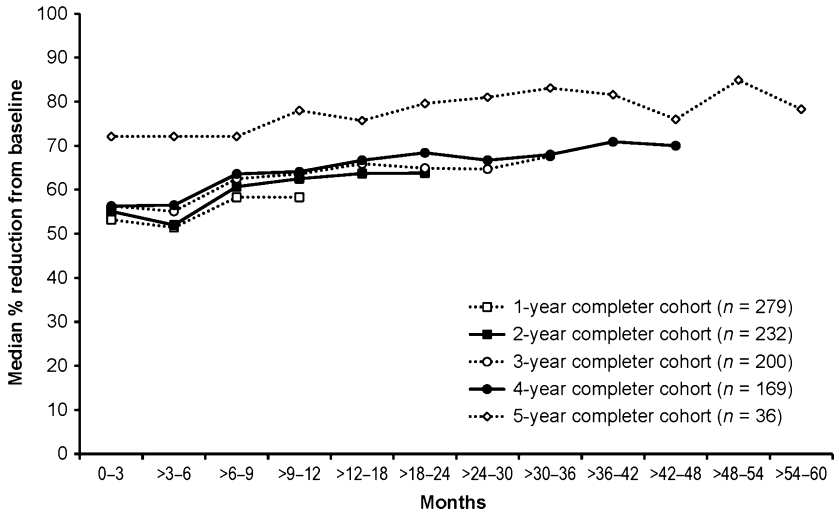

Figure 3. Median percent reduction from baseline in seizure frequency over time by yearly completer cohort. Completer cohorts include patients in the FAS exposed to lacosamide for the duration of the interval. Baseline is defined as the baseline phase from the previous trial. Percent change from baseline = 100 × ([seizure frequency – baseline seizure frequency]/baseline seizure frequency). Median reduction from baseline is presented as a positive number.

Lacosamide monotherapy – Of eight patients who converted to lacosamide monotherapy for ≥12 months, one achieved and maintained seizure-free status for the entire 60-month trial duration and two others maintained seizure-free status during the final 48 and 36 months of the trial. Of the remaining five patients, four remained in the trial for >48 months, three of whom were ≥50% responders.

Discussion

This long-term trial conducted in Europe and Australia provided up to 5.5 years of exposure to lacosamide (100–800 mg/day), demonstrating that lacosamide was generally well tolerated in patients with POS taking up to three concomitant AEDs. More than half of patients (52.9%) were still taking lacosamide after 3 years, consistent with previous long-term OLE trials of lacosamide (6, 7), and 40.6% remained on treatment after 5 years, although it should be noted that not all patients had the opportunity to receive lacosamide for longer than 40 months due to the availability of commercial lacosamide in some countries. Although 57.4% of patients discontinued lacosamide, this should be considered in light of the refractory nature of their epilepsy. It could be anticipated for a population among whom 36.4% had tried ≥7 lifetime AEDs that further changes in medication would be required during long-term follow-up.

Similar to results from shorter term double-blind trials (3–5), nervous system events (e.g., dizziness and headache) were the most common TEAEs reported with long-term lacosamide treatment. Other common TEAEs associated with long-term treatment were related to gastrointestinal disorders and infections (e.g., nasopharyngitis). Many were not considered by the investigators to be related to lacosamide, as they are often reported during long-term studies.

Unlike the more controlled design of a fixed-dose trial, dosage adjustments for both lacosamide (100–800 mg/day) and concomitant AEDs were permitted during this trial to allow investigators to optimize each patient's treatment regimen based on their clinical judgement, and this may have had safety implications that differed from the original double-blind trials. Comprehensive evaluation of laboratory assessments, vital sign measurements, and body weight did not reveal any clinically relevant abnormalities associated with long-term lacosamide.

Treatment-emergent AEs of particular relevance to patients with POS were also reported, although the absence of a comparator in this trial or an epidemiologically similar population for comparison limits the ability to draw definitive conclusions. Specifically, memory impairment, cognitive disorder, increased/decreased weight, rash, and suicide-related TEAEs were each reported by <5% of patients. Although the mechanism of action is not known, AEDs as a drug class may be associated with increased risk of suicidal behaviors and ideation (8). Considering the duration of lacosamide exposure in this study, the incidence of suicide-related TEAEs

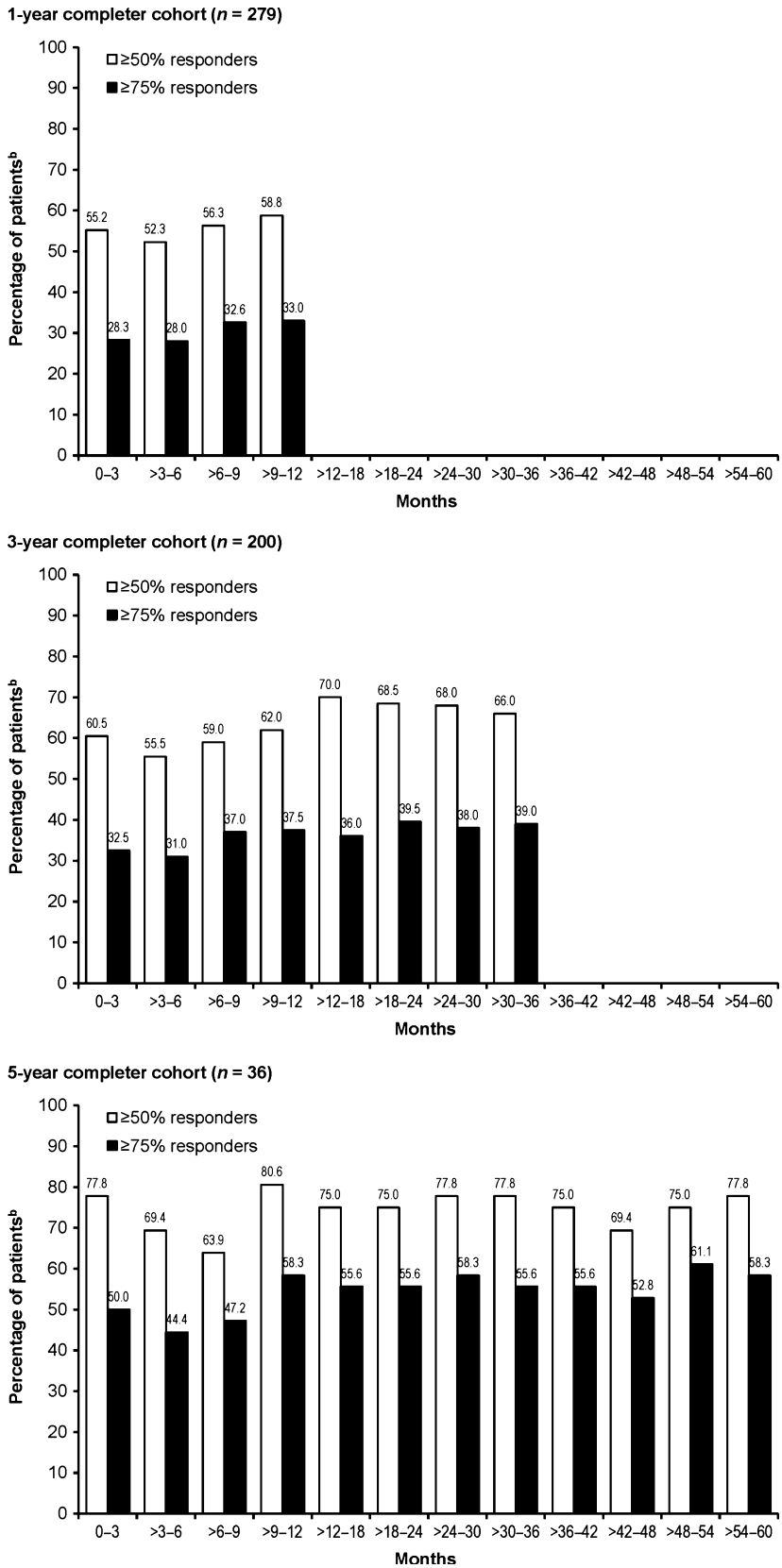

Figure 4. ≥50% and ≥75% responders[a] over time by yearly completer cohort[b]. [a]Responders were defined as patients with at least a 50% or at least a 75% reduction in 28-day seizure frequency during the time interval specified from baseline of the previous trial. [b]Percentages based on the number of patients in the completer cohort with an evaluable responder status during the specified time interval.

was consistent with that expected in this population (9).

Treatment-emergent AEs that led to discontinuation during this trial indicated that no potential safety issues emerge from short-term to long-term lacosamide treatment, with dizziness the most commonly cited TEAE that led to discontinuation. Acknowledging the limitations of cross-study comparisons, the rate of discontinuation due to AEs in this trial fell within the range observed in other AED OLE studies of 1–8 years in duration (6, 7, 10–14). It is difficult to discern differences in tolerability by lacosamide dosage, as discontinuations were analyzed by modal dosage rather than dosage at withdrawal.

Despite being a difficult-to-treat patient population, half of the patients experienced ≥50% reductions in 28-day seizure frequency, and nearly a quarter experienced ≥75% reductions during the open-label treatment period. Patient withdrawals due to lack of efficacy in studies with this type of design can create an 'enriched' population that appears to show increased efficacy over time. To address this issue, data were evaluated by completer cohorts to facilitate evaluation of only patients who completed treatment of the same duration (1, 3, or 5 years). In these analyses, seizure reduction was generally maintained over time (decreased sample size of the longer duration cohorts notwithstanding). In addition, up to 50% of patients in yearly completer cohorts attained meaningful periods of seizure freedom (≥6 months; any seizure type). Up to 54% of the patients enrolled in this OLE trial who experienced SGS during baseline and post-baseline of the double-blind trial achieved freedom from SGS for ≥6 months, indicating that even more severe seizure types could be well managed in these patients. Because the open-label design and flexible dosing of both lacosamide and concomitant AEDs limit data interpretation, efficacy results should be considered descriptive only, as improvements in some patients may have been attributable to changes in concomitant AEDs.

In summary, data from this OLE support the use of lacosamide as a long-term (up to 5.5 years) adjunctive treatment for POS in patients taking up to three concomitant AEDs. Long-term lacosamide was generally well tolerated, and, for most patients within each yearly completer cohort, seizure reduction was maintained over time.

Acknowledgements

The authors acknowledge Anthony Daniels, UCB Pharma, Raleigh, NC, USA, and Maria-Luise Esch, UCB Pharma, Monheim am Rhein, Germany, for clinical project management, and Jennifer Hepker, PhD of PMCG, Chicago, IL, USA, and Steve Dobson of Evidence Scientific Solutions, Horsham, UK, for writing support, which was funded by UCB Pharma.

Conflict of interest

This study was funded by UCB Pharma, Monheim am Rhein, Germany. Dr Rosenow has received honoraria and advisor fees from Eisai; grants, honoraria, and advisor fees from UCB; grants and honoraria from Desitin Pharma; grants and honoraria from Novartis; honoraria from Medtronic; travel expenses from Cerbomed; grants from the European Union; and grants from Deutsche Forschungsgemeinschaft. Dr Menachem has received consultancy fees and/or research grants from UCB, Eisai, Electrocore, Bial, and Wiley Press during the past 18 months. Dr Kelemen has nothing to disclose. Dr Isojarvi was an employee of UCB Biosciences Inc. during the conduct of the study. Ms McShea and Dr Doty are employees of UCB Biosciences Inc.

References

1. VIMPAT® (lacosamide) C-V Prescribing Information. Smyrna, GA, USA: UCB, Inc., 2014.
2. Vimpat (lacosamide) Summary of product characteristics. Brussels, Belgium: UCB Pharma, SA, 2015.
3. Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia 2007;**48**:1308–17.
4. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M et al. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. Epilepsia 2009;**50**:443–53.
5. Chung S, Sperling MR, Biton V et al. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. Epilepsia 2010;**51**:958–67.
6. Rosenfeld W, Fountain NB, Kaubrys G et al. Safety and efficacy of adjunctive lacosamide among patients with partial-onset seizures in a long-term open-label extension trial of up to 8 years. Epilepsy Behav 2014;**41**:164–70.
7. Husain A, Chung S, Faught E, Isojarvi J, McShea C, Doty P. Long-term safety and efficacy in patients with uncontrolled partial-onset seizures treated with adjunctive lacosamide: results from a phase III open-label extension trial. Epilepsia 2012;**53**:521–8.
8. Ferrer P, Ballarin E, Sabate M et al. Antiepileptic drugs and suicide: a systematic review of adverse effects. Neuroepidemiology 2014;**42**:107–20.
9. Food and Drug Administration, Levenson M. Statistical review and evaluation: antiepileptic drugs and suicidality: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 2008.
10. Gil-Nagel A, Brodie MJ, Leroy R et al. Safety and efficacy of ezogabine (retigabine) in adults with refractory partial-onset seizures: interim results from two ongoing open-label studies. Epilepsy Res 2012;**102**:117–21.
11. Hufnagel A, Ben-Menachem E, Gabbai AA, Falcao A, Almeida L, Soares-Da-silva P. Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with

epilepsy: results of a 1-year open-label extension study. Epilepsy Res 2012;**103**:262–9.
12. Rektor I, Krauss GL, Bar M et al. Perampanel Study 207: long-term open-label evaluation in patients with epilepsy. Acta Neurol Scand 2012;**126**:263–9.
13. Uthman BM, Bazil CW, Beydoun A et al. Long-term add-on pregabalin treatment in patients with partial-onset epilepsy: pooled analysis of open-label clinical trials. Epilepsia 2010;**51**:968–78.
14. Wroe SJ, Yeates AB, Marshall A. Long-term safety and efficacy of zonisamide in patients with refractory partial-onset epilepsy. Acta Neurol Scand 2008;**118**:87–93.

Appendix SP774 study investigators

Australia: Sam Berkovic, West Heidelberg, VIC; Michelle Kiley, Adelaide, SA; Terence O'Brien, Parkville, VIC; David Charles Reutens & Wijesekera Udaya Seneviratne, Clayton, VIC; Martin Kevin Robinson, Woodville, SA; Graham John Schapel, Maroochydore, QLD; Ernest Robertson Somerville, Randwick, NSW. *Croatia*: Tomislav Babic & Zdravka Poljakovic, Zagreb; Vida Demarin, Zagreb; Sanja Hajnsek, Zagreb. *Czech Republic*: Michal Bar, Ostrava; Jindriska Buresova, Olomouc; Helena Hojdikova, Hradec Kralove; Petr Marusic, Prague; Evzen Nespor, Prague; Ivan Rektor, Brno; Hana Vacovska, Plzen; Jana Zarubova, Prague. *Finland*: Reetta K Kälviäinen, Kuopio; Tapani Keränen, Tampere; Juha Tapani Korpelainen, Oulu; Salla Liisi Kaarina Lamusuo & Tuula Nylund, Turku. *France*: Arielle Crespel, Montpellier; Philippe Derambure, Lille; Philippe Ryvlin, Bron; Franck Semah, Paris; Michel Tibergé & Luc Valton, Toulouse. *Germany*: Stephan Arnold & Christoph Siebold, Munich; Martin Holtkamp & Bettina Schmitz, Berlin; Holger Lerche, Ulm; Heinz-Joachim Meencke, Berlin; Michael Nitsche & Frithjof Tergau, Göttingen; Felix Rosenow, Marburg/Lahn; Hermann Stefan, Erlangen. *Hungary*: Attila Balogh, Budapest; Péter Halász & Anna Kelemen, Budapest; Agnes Horvath, Szombathely; Sámuel Komoly & István Kondakor, Pecs; András Sólyom, Budapest; László Vécsei, Szeged. *Lithuania*: Milda Endziniene, Kaunas; Vanda Liesiene, Kaunas; Ruta Mameniskiene, Vilnius; Aloyzas Algimantas Skaringa, Vilnius. *Poland*: Anna Czlonkowska, Warsaw; Waldemar Fryze, Gdansk; Jan Kochanowicz, Bialystok; Maria Mazurkiewicz-Beldzinska, Gdansk; Rafal Motyl, Krakow. *Russian Federation*: Anatoly Fedin, Moscow; Alla Guekht, Moscow; Valentina Guzeva, St. Petersburg; Vladimir Karlov, Moscow; Sergey Kotov, Moscow; Andrey Petrukhin, Moscow; Alexander Skoromets, St. Petersburg. *Spain*: Antonio Gil-Nagel, Madrid; Jose Angel Mauri Llerda, Zaragoza; Mercedes Martin Moro, Madrid; Albert Molins, Girona; Juan Carlos Sanchez, Granada; Jose M Serratosa, Madrid. *Sweden*: Elinor Ben-Menachem, Gothenburg; Per Lindström, Stockholm; Birgitta Söderfeldt, Linköping. *UK*: Martin J Brodie, Glasgow; Oliver Charles Cockerell, London; Paul Nicholas Cooper, Salford; Richard Charles Roberts, Dundee; Inder Mohan Singh Sawhney, Swansea; Philip EM Smith, Cardiff.