Accepted: 8 September 2016

DOI: 10.1111/ane.12691

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

Lacosamide and sodium channel-blocking antiepileptic drug cross-titration against levetiracetam background therapy

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Funding information
UCB Pharma

Objective: To assess prospectively the effectiveness of lacosamide (LCM) added to levetiracetam (LEV) after down-titration of a concomitant sodium channel blocker (SCB) among patients with focal epilepsy not adequately controlled on LEV and SCB.

Methods: In this open-label trial, LCM was initiated at 100 mg/day and up-titrated to 200-600 mg/day over 9 weeks; SCB down-titration started when LCM dose reached 200 mg/day. Patients remained on stable LCM/LEV doses for 12 weeks' maintenance (21-week treatment period). The primary outcome was retention rate on LCM.

Results: Due to recruitment challenges, fewer than the planned 300 patients participated in the trial, resulting in the trial being underpowered. Overall, 120 patients (mean age 39.7 years) started and 93 completed the trial. The most frequently used SCBs were lamotrigine (39.2%), carbamazepine (30.8%) and oxcarbazepine (27.5%). Eighty-four patients adhered to protocol and discontinued their SCB after cross-titration, but there was insufficient evidence for 36 patients. Retention rate was 73.3% (88/120) for all patients and 83.3% (70/84) for those with evidence of SCB discontinuation. Seizure freedom for patients completing maintenance was 14.0% (13/93). Discontinuation due to adverse events (6.7%) and lack of efficacy (3.3%) occurred primarily during cross-titration. Most frequently reported adverse events during treatment were dizziness (23.3%), headache (15.0%) and fatigue (8.3%).

Conclusions: In patients with uncontrolled seizures on LEV/SCB, the LCM/LEV combination appeared to be effective and well tolerated. A cross-titration schedule—flexible LCM up-titration, concomitant SCB down-titration and stable background LEV—could present a feasible and practical approach to initiating LCM while minimizing pharmacodynamic interactions with a SCB.

KEYWORDS

antiepileptic drugs, cross-titration, epilepsy, seizures, treatment

1 | INTRODUCTION

Given the large number of available antiepileptic drugs (AEDs) and the even larger number of possible combinations, systematic evaluation of optimal AED combinations is not feasible.[1]

It has been proposed that combination therapy should include selection of drugs with low potential for drug-drug interactions (DDIs) and for amplification of adverse effects, while minimizing total drug load.[2] Combining AEDs based on their mechanism of action can also provide a rational approach to the challenge.[1,3] While the potential

for enhanced neurotoxicity when combining two sodium channel-blocking AEDs was observed over 40 years ago, evidence for enhanced efficacy with specific combinations remains inconsistent.[4-6]

While traditional sodium channel blockers (SCBs) such as phenytoin, carbamazepine and lamotrigine act by inhibiting fast inactivation of the channels, lacosamide (LCM) selectively enhances slow inactivation.[7,8] Post hoc analyses of data pooled from double-blind, placebo-controlled trials suggested that the combination of LCM with a non-SCB might be associated with better tolerability than with a SCB.[9] A retrospective study also highlighted cases of patients who did not tolerate LCM 200-350 mg/day without concurrent reduction of carbamazepine or oxcarbazepine.[10] Levetiracetam (LEV) is a non-SCB AED; therefore, based on their differing mechanisms of action and low potential for DDIs, the combination of LCM and LEV may provide additional therapeutic benefit.

The objective of the trial reported here was to evaluate prospectively the effectiveness of LCM when added to LEV, with cross-titration (discontinuation) of the concomitant SCB among patients with focal epilepsy.

2 | METHODS

This was a phase IIIb, open-label trial conducted across Australia, Europe and the USA (SP0980, NCT01484977). It was conducted in accordance with applicable regulatory and International Conference on Harmonisation Good Clinical Practice requirements, and the ethical principles of the Declaration of Helsinki. National, regional or independent ethics committee in each country approved the trial. All participants provided written informed consent.

The trial had a 4-week screening period, a 21-week treatment period (9-week cross-titration and 12-week maintenance) and a taper/safety period, lasting up to 4 weeks (Figure 1). Patients started LCM at 100 mg/day (50 mg bid), increased to 200 mg/day after 1 week. Over the remaining 8 weeks, the dose was increased in increments of 100 mg/day/week as needed (maximum 600 mg/day). One dose reduction was allowed in case of tolerability issues. SCB down-titration was initiated when patients reached LCM 200 mg/day, the minimum therapeutic dose, and discontinued fully by the end of cross-titration. Lacosamide (and LEV) doses had to remain stable during the 12-week maintenance period. At the end of maintenance, patients choosing not to continue LCM entered a 4-week taper/safety follow-up period.

Patients aged ≥18 years were included if they had a diagnosis of focal epilepsy and, despite treatment with a combination of LEV and a SCB, were still experiencing seizures (at least one seizure/4 weeks within the 8-week retrospective baseline, and at least one seizure during the 4-week prospective baseline/screening period). Patients had to be on stable AED doses for ≥4 weeks before screening. SCBs could be carbamazepine, lamotrigine, oxcarbazepine, phenytoin or eslicarbazepine. Exclusion criteria included previous exposure to LCM, use of an AED other than the current SCB and LEV during the 4 weeks before screening, lifetime or concomitant treatment with felbamate or vigabatrin, primary generalized seizures, status epilepticus within the last year, seizure clustering, simple focal seizures without motor signs or non-epileptic ictal events, progressive central nervous system disease, electrocardiogram (ECG) abnormalities, class III/IV heart failure, sodium channelopathy or myocardial infarction in the previous 3 months. Female participants of childbearing potential were required to use contraception.

The primary outcome was retention rate—percentage of patients who received 21 weeks of LCM treatment, completed the termination visit and had trial medication exposure for at least 144 days. Seizure outcomes included per cent change and ≥50% and ≥75% reduction in

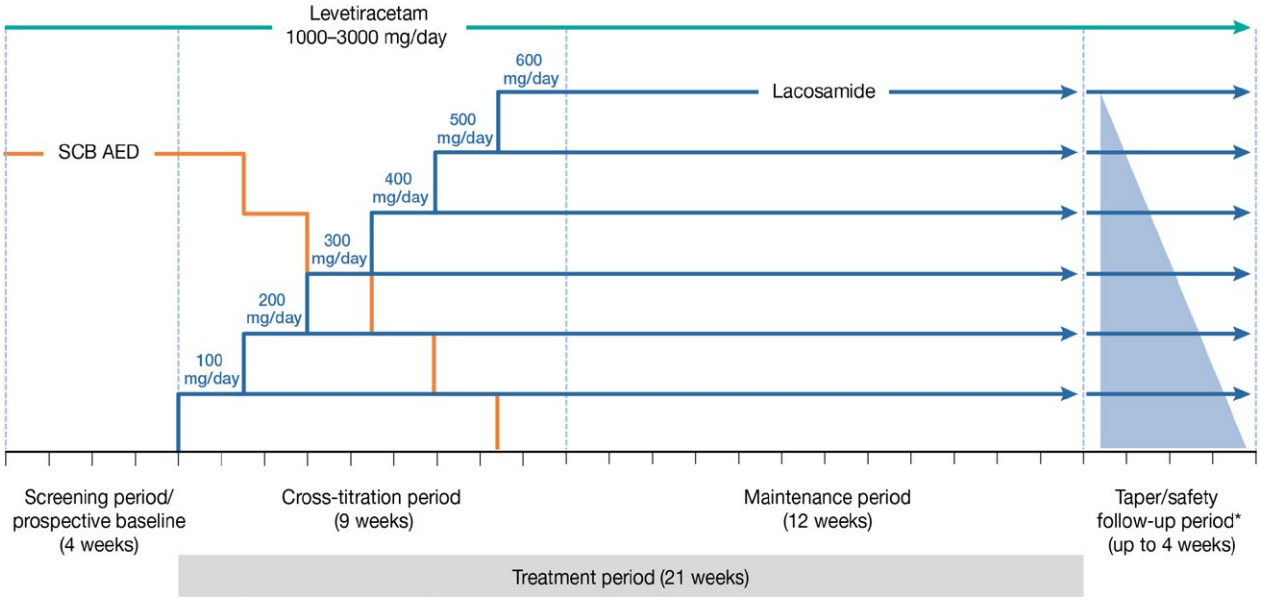

FIGURE 1 Trial design. *Patients could either taper off or continue receiving commercial lacosamide (SCB AED=sodium channel-blocking antiepileptic drug)

28-day focal seizure frequency during the maintenance and treatment periods. Seizure freedom during the maintenance period was calculated as a percentage based on the number of patients who completed the maintenance period. A post hoc analysis was conducted to evaluate the effectiveness of LCM among patients treated within the approved dose range of ≤400 mg/day.

Patients' health-related quality of life (HRQoL) was evaluated using the Quality of Life in Epilepsy questionnaire (QOLIE-31-P), a 38-item questionnaire that reports HRQoL in seven domains.[11,12] Patients completed the questionnaire on the first day of the trial and at the end of maintenance or at trial exit if they discontinued. Patients and physicians also provided an overall assessment of change in health status using the Patient's Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC), respectively. Safety was evaluated by monitoring AEs.

As fewer than the planned 300 patients were recruited, the trial lacked sufficient power to detect a 50% reduction in the all-cause discontinuation rate; therefore, all analyses are exploratory in nature. Analyses of the primary and all safety outcomes were based on the safety set (SS, all participants who took at least one dose of LCM). Analyses of other seizure outcomes were based on the full analysis set (FAS, participants in the SS who had at least one seizure diary data assessment during treatment) and the per protocol set (patients who fully discontinued their SCB AED at the end of titration). A post hoc analysis was conducted to evaluate safety and seizure outcomes among patients who were exposed to LCM ≤400 mg/day (modified FAS, mFAS). The primary as well as seizure outcomes were analysed using descriptive statistics, generated using SAS® version 9.1 or higher.

3 | RESULTS

Overall, 147 patients were screened and 120 enrolled; 93 (77.5%) patients completed all trial assessments, while 27 (22.5%) discontinued (Figure 2). Of the 120 patients, 118 had at least one efficacy assessment and were included in the FAS. According to trial protocol, patients should have discontinued their SCB by the start of maintenance. While most patients adhered to the protocol, there was insufficient evidence that 36 patients had stopped taking their SCB AED in time, or at all. Therefore, these patients were not considered to have adhered to protocol, even if the dose of the SCB AED had been partially reduced. Of these 36 patients, 20 completed the trial. All patients, whether they discontinued their SCB or not, were included in the efficacy analysis (intention-to-treat population or FAS). In the subgroup of 51 patients who took LCM ≤400 mg/day (mFAS), 33 discontinued while 18 continued to take their SCB at the end of cross-titration. Thirty-seven patients (29/33 and 8/18) completed the maintenance period.

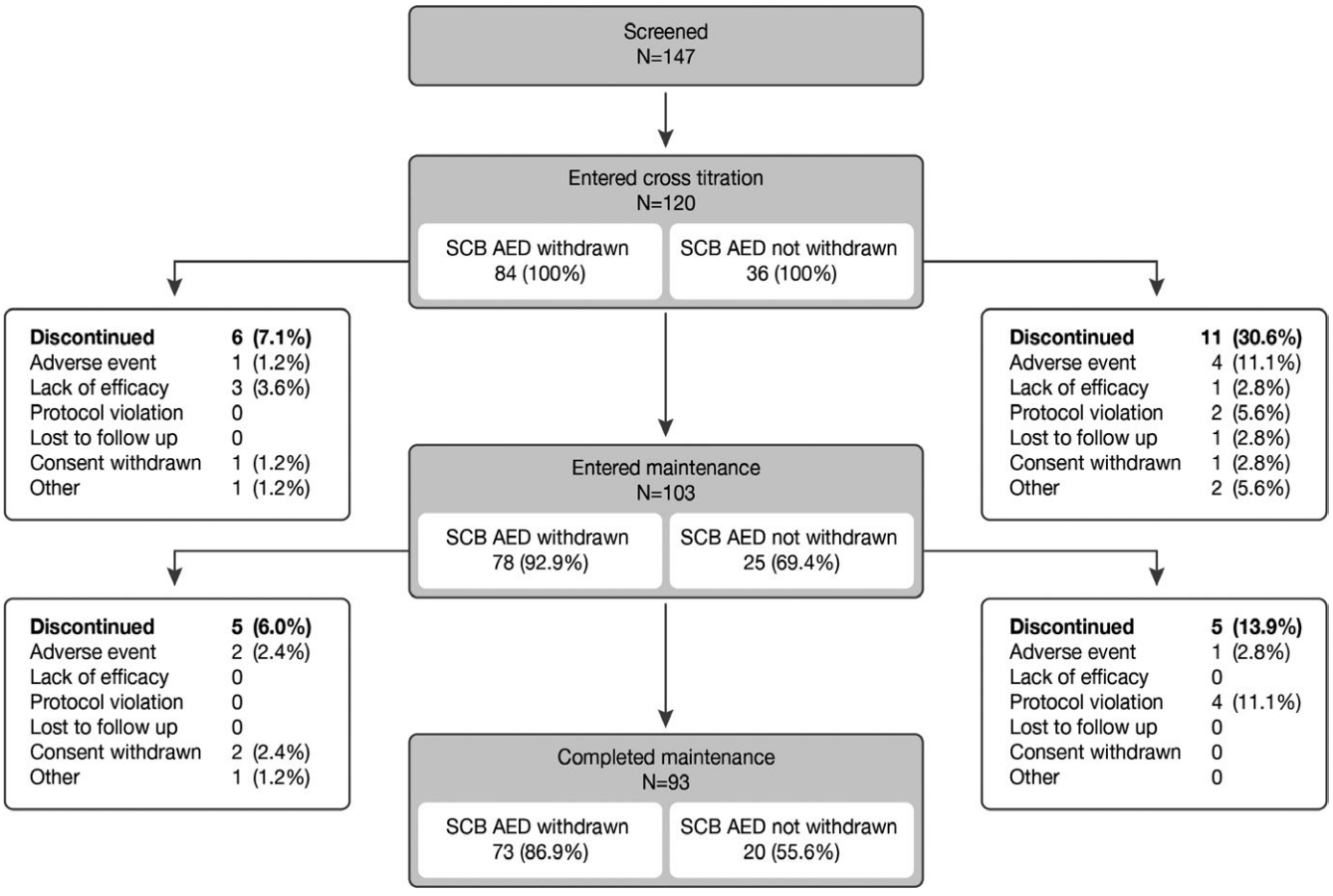

FIGURE 2 Trial disposition

Demographic and baseline epilepsy characteristics are summarized in Table 1. Median LCM dose for the overall population was 500.0 mg/day (198.7-600.0 mg/day) during the maintenance period and 389.9 mg/day (66.7-536.1 mg/day) during the treatment period. Corresponding values were 499.6 mg/day (198.7-600.0 mg/day) and 400.6 mg/day (66.7-536.1 mg/day), respectively, for those who discontinued their SCB. In the subgroup who took LCM ≤400 mg/day, the median dose was 398 mg/day (199-400 mg) during the maintenance period and 285 mg/day (67-375 mg) during the treatment period.

Retention rate at the end of the 21-week treatment period was 73.3% for the overall population (N=120; SS) and 83.3% for those who discontinued their SCB (n=84, per protocol population). The median per cent reduction from baseline in 28-day focal seizure frequency was 45.80% during treatment and 64.06% during the maintenance period for the FAS (n=118). Corresponding values for the per protocol population subpopulation that discontinued their SCB were 46.75% and 50.57%, respectively.

In the FAS, 45.8% of patients reported ≥50% reduction and 27.1% reported ≥75% reduction from baseline in 28-day focal seizure frequency during the treatment period. Corresponding values for the maintenance period were 47.5% and 37.3%, respectively (Figure 3). Among patients who discontinued their SCB, 47.6% reported ≥50% reduction and 29.8% reported ≥75% reduction from baseline in 28-day focal seizure frequency during the treatment period. During maintenance, corresponding values were 47.6% and 38.1%, respectively. Seizure freedom among patients who completed the maintenance period was 14.0% in the FAS and 13.7% in the per protocol population (Figure 3). Results of the post hoc analysis showed that compared with the overall population, there was a trend towards better seizure-related outcomes among patients who took LCM ≤400 mg/day, especially among those who discontinued their SCB (Figure 3).

At baseline, the mean total score for QOLIE-31-P was 59.50 (n=116). At Visit 7 (or early trial termination), the total score showed a mean improvement of 3.91±14.39 points (n=113). All subscale scores also increased from baseline to Visit 7 (Figure 4). A mean improvement of >5 points was observed for energy/fatigue (5.90±21.42), QoL (5.35±18.36) and daily activities/social functioning (5.04±24.52). In the subgroup who took LCM ≤400 mg/day, the mean total baseline QOLIE-31-P score was 59.29 (n=50). At Visit 7, the total score showed a mean improvement of 3.07±13.06 points (n=48) (Figure 4). There were slight differences in the changes in the subscales between the two patient populations. Improvement in seizure worry and medication effects tended to be greater among patients taking ≤400 mg/day, while the improvement in daily activities and energy/fatigue tended to be greater in the overall population.

Most patients (80.9%) reported improvement in health status based on the results of the PGIC. Similarly, for CGIC, investigators reported that most patients (81.7%) had showed an improvement. The proportion of patients showing a worsening in health status was also similar based on the PGIC and CGIC (12.2% and 10.4%, respectively).

Ninety patients (75.0%; SS) experienced TEAEs during the treatment period (Table 2). The most commonly reported were dizziness (23.3%), headache (15.0%) and fatigue (8.3%). The incidence of TEAEs was substantially higher during cross-titration than during

TABLE 1 Demographic and baseline epilepsy characteristics (safety set)

	N=120
Mean age, years (SD)	39.7 (12.6)
Age, n (%)	
≤18 years	1 (0.8)
18 to <65 years	114 (95.0)
≥65 years	5 (4.2)
Sex, n (%)	
Male	46 (38.3)
Female	74 (61.7)
Body mass index, kg/m^2, mean (SD)	27.00 (6.45)
Ethnicity, n (%)	
American Indian/Alaskan Native	1 (0.8)
Asian	3 (2.5)
Black	8 (6.7)
White	96 (80.0)
Other/mixed	12 (10.0)
Time since first diagnosis, years	
Mean (SD)	19.89 (15.60)
Median (range)	16.22 (0.5-58.3)
Seizure history, n (%)	
Focal seizures	120 (100)
Simple focal with	
Motor symptoms	42 (35.0)
Somatosensory symptoms	12 (10.0)
Autonomic symptoms	5 (4.2)
Psychic symptoms	7 (5.8)
Complex focal	90 (75.0)
Focal evolving to secondarily generalized	82 (68.3)
Baseline seizure frequency per 28 days	
Mean (SD)	11.38 (16.50)
Median (range)	6.02 (1.7-112.0)
Number of concomitant AEDs at baseline,[a] n (%)	
0	1 (0.8)
1	1 (0.8)
2	115 (95.8)
3	3 (2.5)
Concomitant AED use (>10%), n (%)	
Levetiracetam	120 (100)
Lamotrigine	47 (39.2)
Carbamazepine	37 (30.8)
Oxcarbazepine	33 (27.5)
Vagus nerve stimulation, n (%)	
Yes	6 (5.0)
No	114 (95.0)

[a]Taking 0, 1 or 3 concomitant AEDs was against the protocol.

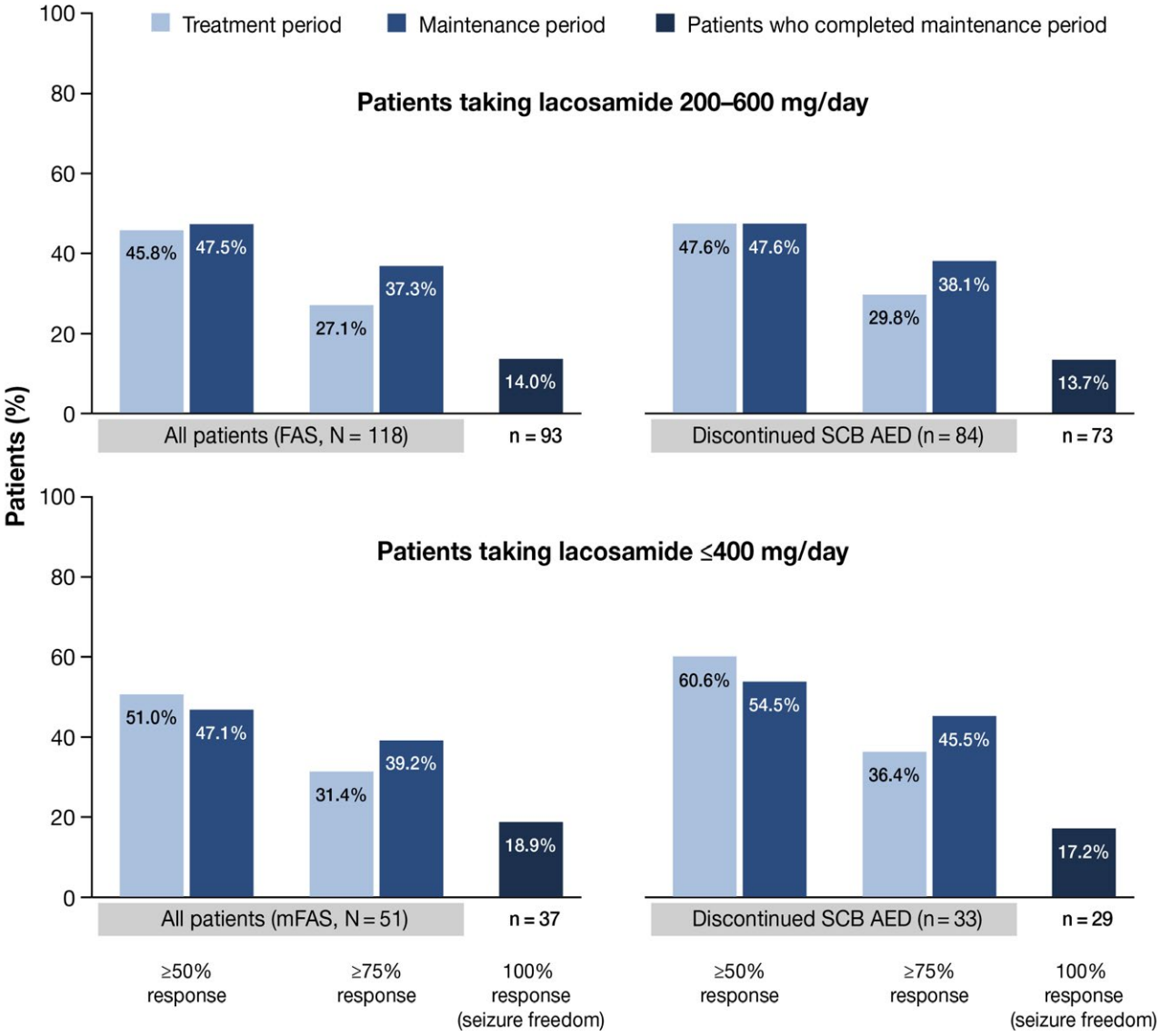

FIGURE 3 Responder rates during the treatment and maintenance periods among patients taking lacosamide doses 200-600 mg day (top panel) and among those taking lacosamide doses ≤400 mg/day (bottom panel). Seizure freedom was evaluated during the maintenance period only, and included patients who completed the maintenance period (FAS=full analysis set; mFAS=modified FAS; SCB AED=sodium channel-blocking antiepileptic drug; PP=per protocol; mPP=modified PP).

maintenance. Overall, 77 of 120 (64.2%) patients experienced 225 TEAEs during cross-titration, while 42 of 103 (40.8%) patients experienced 95 TEAEs during maintenance. During cross-titration, the most common TEAEs were dizziness (20.8%), headache (11.7%), fatigue (7.5%) and nausea (5.8%). The incidence of these TEAEs decreased substantially during maintenance; corresponding values among the 103 patients who entered maintenance were 4.9%, 5.8% and 1.9%, respectively. Nausea was not experienced by any of the patients during maintenance.

Most (63.3%) TEAEs reported during treatment were of mild intensity. Severe TEAEs were reported by 6.7% of patients; only severe migraine was reported by >1 patient (2/120 patients, 1.7%). Similarly, most (58.3%) TEAEs were not LCM-related as determined by the investigator. Of the TEAEs that were LCM-related, the most frequent were dizziness (15.8%), fatigue (6.7%), nausea and somnolence (4.2% each) and diplopia and headache (3.3% each).

Seven patients (5.8%) reported 15 serious TEAEs during the treatment period; only pneumonia was experienced by more than one patient (2/120, 1.7%). Most serious TEAEs occurred during cross-titration (five patients); only two patients experienced serious TEAEs during maintenance, while one patient experienced a serious TEAE during follow-up. Eight (6.7%) patients discontinued due to TEAEs during the treatment period. The most common were those coded to convulsion (2.5%) and suicidal ideation (1.7%), and most were LCM-related as determined by the investigator; however, none were serious or severe in intensity. Most patients discontinued during cross-titration (7/120 patients, 5.8%), including two of the three who experienced TEAEs coded to convulsion.

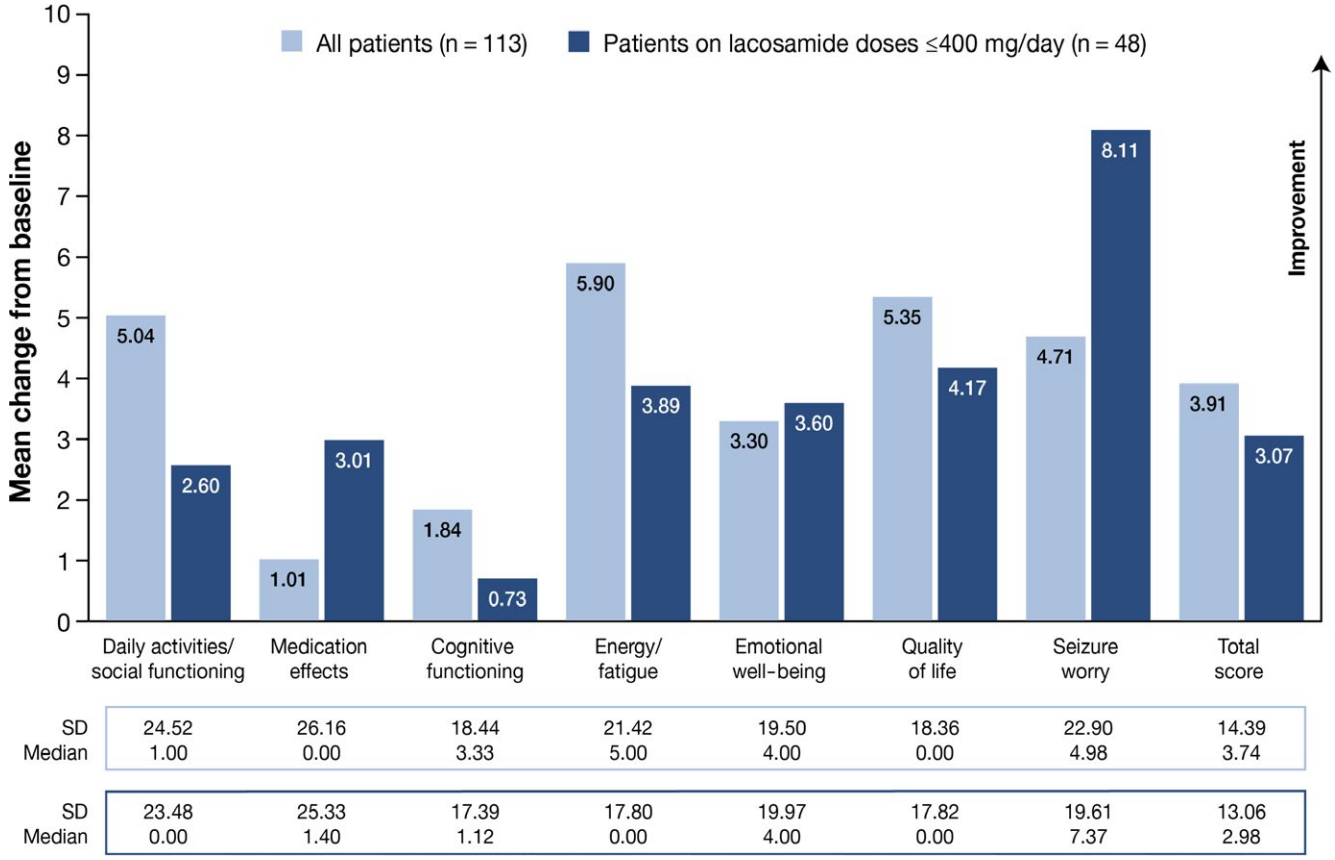

FIGURE 4 Mean change in QOLIE-31-P total and subscale scores from baseline to Visit 7 or early trial termination (SD=standard deviation)

TABLE 2 Summary of treatment-emergent adverse events (TEAEs) reported during the treatment period and incidence of TEAEs reported by ≥3% of patients during the cross-titration and maintenance periods (safety set)

TEAEs, n (%)	Treatment period N=120
Any TEAE	90 (75.0)
Drug-related TEAEs	46 (38.3)
Discontinuation due to TEAEs	8 (6.7)

TEAEs, n (%)	Cross-titration period (N=120)	Maintenance period (N=120)
Dizziness	25 (20.8)	5 (4.9)
Headache	14 (11.7)	6 (5.8)
Fatigue	9 (7.5)	2 (1.9)
Nausea	7 (5.8)	0
TEAEs coded to convulsion	5 (4.2)	2 (1.9)
Somnolence	5 (4.2)	0
Insomnia	4 (3.3)	1 (1.0)
Fall	4 (3.3)	0
Pruritus	4 (3.3)	0

Three (5.9%) of 51 patients who were treated with LCM ≤400 mg/day discontinued due to TEAEs. The main TEAEs reported for the overall population, dizziness, headache and fatigue, were numerically less frequent in the subgroup: 23.3% vs 15.7%, 15.0% vs 11.8% and 8.3% vs 7.8%, respectively. Other TEAEs reported by ≥5% of patients in the subgroup were nausea, urinary tract infection, fall and depression (5.9% each).

No clinically relevant changes in clinical laboratory values, vital signs, ECG and physical/neurological examination parameters were reported.

4 | DISCUSSION

The approval of LCM as adjunctive therapy in focal epilepsy was based on the results of three pivotal trials,[13-15] all followed by open-label extensions.[16-18] In the pivotal trials, patients with highly refractory disease received LCM in a fixed titration scheme added to a variety of AEDs—up to 82% had a SCB in their treatment regimen.[9,19] Post hoc analyses based on the mechanism of action of patients' concomitant AEDs suggested that LCM therapy resulted in significant seizure reduction relative to placebo, regardless of presence/absence of SCBs.[9] Results also suggested a potential for better tolerability and efficacy outcomes, especially at higher LCM doses, among patients not taking

concomitant SCBs.[9] Reports from clinical practice suggested that early cross-titration of the SCB when initiating adjunctive LCM could help mitigate AEs and improve retention.[10,20]

Given the post hoc nature of the previous analyses and the numerous caveats associated with the pivotal trials—notably a forced titration schedule, fixed dosing and the presence of ≥2 AEDs in most patients' baseline treatment regimen—the current trial was conducted to evaluate prospectively the effectiveness of LCM in combination with a single AED following withdrawal of the concomitant SCB. The titration schedule was designed to facilitate conversion from a SCB to LCM by allowing the dose of LCM to be up-titrated with concurrent down-titration of the SCB. Furthermore, the trial was designed to closely reflect clinical practice, where drug doses are adjusted based on patients' clinical response.

During the conduct of the trial, challenges in recruitment became apparent. Inclusion criteria placed a practical restriction on the patient population—patients had to be experiencing focal seizures despite treatment with the very specific combination of LEV and a single SCB. Given the large number of combinations available with the currently marketed AEDs, the required specific combination was a strong limiting factor in recruitment to the trial. Consequently, given the slow enrolment, it was decided to terminate the trial after enrolment of 120 patients, instead of the planned 300. As the sample size was smaller than that required based on power calculations, the trial did not have sufficient power to detect statistical differences in the all-cause discontinuation rate. Therefore, all analyses reported here are descriptive. A further limitation of the trial was that some patients did not appear to follow the protocol. At the end of the cross-titration period, patients were required to stop taking their SCB; while they may have stopped, there was insufficient documented evidence for 36 of them. Although the concomitant SCB AED could have been partially reduced, a conservative approach was taken in the analysis by classifying all patients without evidence of full discontinuation as non-protocol adherent.

With these caveats in mind, results showed that combination therapy with LCM and LEV following SCB discontinuation was associated with effective seizure control and favourable tolerability. The overall retention rate was 73.3% (88/120), while in the subpopulation of patients with sufficient evidence of SCB discontinuation it was 83.3% (70/84). The effectiveness of the combination was also evident from seizure-freedom rates. In the overall population, 14.0% of patients remained seizure-free during the maintenance phase; among those treated with LCM ≤400 mg/day, the corresponding value was 18.9%. These rates compared favourably with those obtained in the pivotal trials (3.3% and 4.8% for patients treated with LCM 400 and 600 mg/day, respectively).[19] It is important to note, however, that comparisons of the results should be interpreted with caution, given different trial designs.

Results for all seizure-related outcomes tended to be higher among patients who took LCM doses ≤400 mg/day and discontinued their SCB AED. This was in comparison with both the overall and the subgroup populations. A potential explanation for this observation is the real-life setting of the trial, which allowed for flexible dose titration. Consequently, patients with less treatment refractory epilepsy responded fully to lower doses, while those with more severe or refractory disease required higher doses to achieve similar levels of seizure control. Use of low doses is important in combination therapy, since the greater the drug burden, the greater the risk of AEs and DDIs and consequent treatment discontinuation.[21-23] Indeed, the toxicity burden of overtreatment can have a greater negative impact on patients than the disease itself.[24]

The total and all QOLIE-31-P subscale scores increased from baseline to trial end, indicating improvement in patients' HRQoL. The LCM and LEV combination was well tolerated. The most common TEAEs were dizziness, headache and fatigue, and the majority were reported during cross-titration (64.2% vs 40.8% during maintenance). The incidence of these three TEAEs declined substantially during maintenance. Discontinuation rate due to TEAEs was 6.7% (8/120) in the current trial, which is similar to that observed in the subpopulation of patients in the pivotal trials that did not take SCBs. Discontinuation rates due to TEAEs—7.8%, 7.2% and 6.9% for the 200, 400 and 600 mg/day groups, respectively—were not dose-related in that subpopulation.[9] Corresponding values for patients whose treatment regimen included SCBs were 5.5%, 14.4% and 31.0%.[9] No clinically relevant changes in vital signs, ECG and physical examination parameters were observed. Overall, TEAEs reported during this trial were consistent with the known safety profile of LCM,[25] and no new safety signals were detected. Recent data also indicate that adjunctive LCM does not affect information processing speed, the most sensitive function for cognitive side effect of AEDs, confirming observations in healthy volunteers [26,27]

Results of this trial suggest the feasibility of flexible dosing and a cross-titration schedule when initiating treatment with LCM. A similar schedule was employed in another prospective, open-label study, but with a smaller number of patients (N=23).[20] Over a 5-week cross-titration period, LCM dose was increased in weekly increments of 100 mg/day while the dose of the concomitant SCB was reduced and the dose of baseline concomitant non-SCB was maintained. Investigators reported effective seizure control with a reduction in CNS-related side effects through the subsequent 12 months of treatment with LCM doses up to 800 mg/day. In the current trial however, lower LCM doses were used—the median dose for the overall population was 500.0 mg/day during the maintenance period and 389.9 mg/day during the treatment period. Corresponding values were 499.6 and 400.6 mg/day, respectively, for those who discontinued their SCB. Lower median modal doses during the treatment period are probably due to patients discontinuing before reaching an efficacious dose. The median dose of LEV remained stable at 2000 mg/day for all patients during the treatment period.

While the number small sample size precluded statistical analyses, results described here show that treatment with a combination of LCM and LEV after down-titration of a SCB was associated with high retention and seizure-freedom rates. The combination was also well tolerated, as shown by the low discontinuation rate due to AEs (6.7% in the overall population and 3.6% among those who discontinued their SCB). Based on the proposed tenets of combination therapy [2] and the results of this trial, the addition of LCM to LEV could present an acceptable therapeutic approach. Furthermore, for patients who

still experience seizures despite combination therapy with a SCB, the cross-titration schedule described here, as well as by others,[10,20] could offer a practical approach to initiating LCM while minimizing potential pharmacodynamic interactions.

ACKNOWLEDGEMENTS

The authors express their gratitude to the patients who agreed to take part in the trial. The authors acknowledge the contribution of the investigators and Kimberly Doggett and Petrina Wall (clinical trial managers, UCB Pharma). The authors also thank Barbara Pelgrims, UCB Pharma, who oversaw the development of this publication. Writing support was provided by Azita Tofighy, funded by UCB Pharma.

CONFLICTS OF INTEREST

Michel Baulac has received compensation for consulting and speaking services from UCB Pharma, Eisai, GSK and ViroPharma. William Byrnes, Paulette Williams, Elizabeth Webster, Marc De Backer, Simon Borghs and Peter Dedeken are employees of UCB Pharma.

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How to cite this article: Baulac, M., Byrnes, W., Williams, P., Borghs, S., Webster, E., De Backer, M. and Dedeken, P. Lacosamide and sodium channel-blocking antiepileptic drug cross-titration against levetiracetam background therapy. *Acta Neural Scand*. 2017;135:434–441.