Received: 29 April 2019 | Revised: 12 May 2019 | Accepted: 31 May 2019

DOI: 10.1002/epi4.12346

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia Open® Open Access

Changes in drug load during lacosamide combination therapy: A noninterventional, observational study in German and Austrian clinical practice

Fritjof Reinhardt[1] | Yvonne G. Weber[2] | Thomas Mayer[3] | Gerhard Luef[4] | Lars Joeres[5] | Frank Tennigkeit[5] | Peter Dedeken[6]* | Marc De Backer[6] | Scarlett Hellot[5] | Thomas Lauterbach[5]† | Tanja Webers[5] | Stephan Arnold[7]

[1]NeuroNetwork of Lusatia of the Technical University of Brandenburg Cottbus-Senftenberg, Senftenberg, Germany

[2]Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

[3]Saxon Epilepsy Center Radeberg, Radeberg, Germany

[4]Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

[5]UCB Pharma, Monheim am Rhein, Germany

[6]UCB Pharma, Brussels, Belgium

[7]Department of Neurology, Schön Klinik Vogtareuth, Vogtareuth, Germany

Correspondence
Stephan Arnold, Department of Neurology, Schön Klinik Vogtareuth, Krankenhausstraße 20, 83569 Vogtareuth, Germany.
Email: SArnold@Schoen-klinik.de

Funding information
UCB Pharma

Abstract

Introduction: Effects of antiepileptic drug (AED) load changes in patients with focal seizures have not been well evaluated.

Methods: SP1065 (NCT01673282) was a noninterventional, prospective, observational study conducted in a clinical practice setting. Patients (aged ≥18 years) with focal seizures were enrolled within 7 days of being prescribed adjunctive lacosamide. Observation period was ~6 months. Drug load was assessed using percentage change in ratio of actual prescribed dose and World Health Organization defined daily dose (DDD) for concomitant AEDs and all AEDs (including lacosamide). Subgroups were defined for patients with at least one concomitant sodium channel–blocking AED (SCB [+]) and those without (SCB [−]).

Results: A total of 311 patients were assessed for safety, 302 for measurement of drug load, and 240 for effectiveness. Ratio of AED dose to DDD decreased for concomitant AEDs (−9.6%) and increased for all AEDs (including lacosamide; 15.5%). Median reduction in focal seizure frequency per 28 days was 100% (range: −100, 2275.8). 70.4% and 61.7% of patients had a ≥50% or ≥75% reduction in seizure frequency, respectively; 50.8% became seizure-free. In the SCB (+) subgroup (n = 149), ratio of AED dose to DDD decreased for concomitant AEDs (−15.0%) and increased for all AEDs (10.7%). In the SCB (−) subgroup (n = 153), ratio of AED dose to DDD decreased for concomitant AEDs (−4.4%) and increased for all AEDs (20.2%). Fifty-seven patients (18.3%) reported ADRs, most commonly dose >400 mg/d (7.1%). Seventeen patients (5.5%) had ADRs leading to discontinuation.

Significance: Addition of lacosamide resulted in reduction of concomitant AED drug load regardless of whether concomitant AEDs were SCB (+) or SCB (−). These

*At time of study participation, currently Heilig Hart Hospitaal, Lier, Belgium.

†At time of study participation, currently freelance consultant.

results indicate that addition of lacosamide in patients with focal seizures could allow clinicians to withdraw or reduce the dose of less well-tolerated or less effective AEDs.

KEYWORDS
antiepileptic drug, sodium channel blocker, combination therapy, drug load, seizure frequency

1 | INTRODUCTION

While the majority of patients with epilepsy will achieve seizure freedom with a single antiepileptic drug (AED),[1] patients with drug-resistant focal epilepsy will generally require treatment with more than one AED.[2] However, antiepileptic polytherapy is commonly thought to result in reduced tolerability[3] and most physicians would aim to treat newly diagnosed epilepsy patients with a single AED.[4] In clinical studies to date, the advantage of monotherapy over polytherapy in terms of tolerability does not appear to be completely clear-cut and may depend on the number, dose, and type of concomitant AED. Studies examining the effects of reducing concomitant AEDs or comparing AED monotherapy with polytherapy have had mixed results. In a study of patients who were undergoing lacosamide titration, a proportion of patients (55.7%) underwent planned reduction of concomitant AEDs. Patients who reduced the number of concomitant AEDs had a lower incidence of adverse events (AEs) than those who did not reduce concomitant AEDs without significant differences in seizure outcomes between groups.[5] Conversely, when Deckers and colleagues compared carbamazepine monotherapy with a combination of carbamazepine and valproate in a randomized, double-blind trial, they observed no statistically significant differences in seizure reduction, overall incidence of AEs, or discontinuation because of AEs.[6] Similarly, an observational study of patients who had failed one AED monotherapy revealed no differences in tolerability, retention time, hospital admissions, days off work and off school, or quality of life between patients receiving an alternative monotherapy and those receiving polytherapy.[7] Efficacy, tolerability, and quality of life were also comparable between monotherapy and polytherapy groups in an open-label, randomized controlled trial conducted by Semah and colleagues.[8]

The lack of consensus regarding the effects of AED polytherapy is further complicated by the fact that most trials comparing monotherapy and polytherapy have concentrated on the number of AEDs in the treatment regimen without considering the doses of each drug. A systematic literature review has suggested that AED toxicity may be related to the overall AED drug load in patients on polytherapy rather than the number of concomitant AEDs.[9] Drug load can be quantified using the ratio of the actual prescribed dose and the World Health Organization (WHO) defined daily dose (DDD). Limited information is available regarding the effect of AED drug load on outcomes and tolerability. As this is an important clinical consideration, assessment of the effects of drug load should be performed under conditions that emulate those seen in clinical practice. Drug load effects cannot be accurately measured in randomized controlled trials due to fixed titration schedules and maintenance doses and because concomitant AEDs and doses have to remain stable. Therefore, measuring drug load is only possible in noninterventional studies where dose adaptations of the test drug as well as the concomitant AEDs are fully flexible. Drug load has rarely been carefully assessed in noninterventional studies.

Key Points

- This study reflects current epilepsy clinical practice in Germany and Austria
- Addition of lacosamide resulted in good effectiveness and tolerability
- Addition of lacosamide resulted in reduction of concomitant AED drug load

Lacosamide is a functionalized amino acid that selectively enhances slow inactivation of voltage-gated sodium (Na_v) channels, without any effects on fast inactivation.[10] It is currently approved for the treatment of focal (partial-onset) seizures with or without secondary generalization in the European Union[11] and in the United States for patients 4 years of age and older.[12]

This observational study explored changes in drug load and seizure frequency when patients added lacosamide to epilepsy treatment regimens with and without sodium channel–blocking AEDs (SCBs) in German and Austrian clinical practice.

2 | METHODS

2.1 | Study design

This was a noninterventional, prospective, observational study conducted in a daily clinical practice setting in Germany and Austria (SP1065; NCT01673282). This study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and local laws. Additional

reviews were performed by central or local independent ethics committees or institutional review boards. All patients (or their legal representatives) signed a patient data consent form before enrollment. The study was conducted between July 2012 and July 2015. The planned Observation period was ~6 months and comprised four anticipated visits to a physician; firstly at Baseline, an optional visit or phone call during weeks 2-6 of treatment, followed by visits at month 3 and month 6. As this was a noninterventional study, treatment choices were made independent of the study by the treating physician and were consistent with German or Austrian treatment guidelines and local marketing authorization for lacosamide.

2.2 | Patients

This study included patients aged ≥18 years with a diagnosis of epilepsy with focal seizures (with or without evolution to bilateral tonic-clonic seizures). All enrolled patients had experienced at least one seizure in the 3 months before starting lacosamide and must not have received lacosamide for more than 7 days before study entry. There were no predefined exclusion criteria.

2.3 | Outcome measures

The primary outcome measure was the percentage change in the ratio of actual prescribed dose and WHO DDD[13] for the drug load of concomitant AEDs from Baseline to the end of the Observation period. The drug load was calculated as the sum of ratios of dose and DDD for all AEDs at the respective time point. An increase in the ratio indicated an increase in drug load. Other variables included: the incidence of concomitant AED usage; change in the ratio of dose and DDD for all AEDs (including addition of lacosamide) from Baseline to the end of the Observation period; the percent change in focal seizures per 28 days from Baseline to the end of the Observation period; the proportion of patients with a ≥50% or ≥75% reduction in focal seizures per 28 days from Baseline; and the proportion of patients achieving seizure freedom at the end of the Observation period, that is, proportion of patients who had no seizures since the previous visit. Seizure frequency was documented at sites according to routine clinical practice. Baseline seizure frequency was based on 3-month historical seizure count; for all other visits, the time since the previous visit was considered. Seizure frequency data were normalized to 28-day periods. Safety and tolerability were assessed using the incidence of adverse drug reactions (ADRs; AEs considered by the investigator to be related to lacosamide treatment) as reported spontaneously by the patient or observed by the physician, and patient withdrawals resulting from ADRs. As predefined in the study protocol, any dose higher than the maximum approved dose of 400 mg/d (off-label use) had to be reported as an ADR irrespective of whether the event resulted in clinical symptoms.

2.4 | Analysis

The change in the ratio of dose and DDD as well as all safety and efficacy variables were summarized using descriptive statistics. Safety variables were analyzed using the safety set (SS; all patients who received at least one dose of lacosamide). The primary outcome measure and variables related to the ratio of dose and DDD were analyzed using the full analysis set (FAS; all patients in the SS who had data allowing calculation of the ratio of dose and DDD at Baseline and at one or more post-Baseline visits). Data for the primary variable are also presented for the modified FAS (mFAS; patients in the FAS who only received adjunctive lacosamide at the approved dose of ≤400 mg/d [no monotherapy] and did not discontinue lacosamide before end of study), for patients based on time since epilepsy diagnosis (<10 years or ≥10 years), and for patients aged <65 years or aged ≥65 years at date of informed consent. Effectiveness variables are presented for the mFAS.

Two subgroups of patients were defined: those adding lacosamide to at least one Baseline AED that was recognized as a sodium channel–blocking AED (SCB [+] group: carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, lamotrigine), and those adding lacosamide to a regimen of other concomitant AEDs (SCB [−] group). Patients were assigned to these groups based on their concomitant AED regimen at Baseline and remained in these groups regardless of any changes to their concomitant AEDs. Results are presented separately for the overall population and for patient subgroups. Exploratory statistical testing was performed post hoc to compare the Baseline characteristics between patients in the SCB (+) and SCB (−) group. A Cochran-Mantel-Haenszel test was performed to compare the number of concomitant AED groups at Baseline between SCB subgroups. Wilcoxon rank-sum tests were used to compare time since first diagnosis and Baseline focal seizure frequency between SCB subgroups. All reported *P*-values are nominal.

The sample size was based on the difference of percentage change in the ratio of dose and DDD between SCB (+) and SCB (−) groups from Baseline to the end of the Observation period. A difference of 20% was assumed as a reasonable target. Taking into account data from a previous study,[14] 140 evaluable patients per group would provide 80% power to detect a 20% difference at 5% significance level. Assuming that ~25% of included patients would not be evaluable for efficacy (missing data as observed in previous noninterventional studies), 374 patients were planned to be included to obtain 280 evaluable patients.

All available data were used for analysis and missing data of variables were not substituted. However, imputations were

done for missing or partial dates in order to use the available data as completely as possible.

3 | RESULTS

3.1 | Patient disposition and characteristics

Overall, 315 patients enrolled and 311 were included in the SS. A total of 154 patients (49.5%) had an epilepsy duration of ≥10 years and 58 patients (18.6%) were aged ≥65 years (Table 1; Table S1). A total of 252 patients (81.0%) completed the study and 59 discontinued treatment (Figure 1). The most common primary reasons for discontinuation were lost to follow-up (6.8%), ADR to lacosamide (4.5%), and lack of efficacy (3.5%). The FAS comprised 302 patients, and 240 patients were included in the mFAS.

Of the 311 patients in the SS, 153 received lacosamide in combination with SCB (+) AEDs at Baseline, of whom 120 (78.4%) completed the study. A total of 158 patients received SCB (−) AEDs at Baseline, of whom 132 (83.5%) completed the study (Figure 1). Patients in the SCB (+) subgroup had a longer time since diagnosis than patients in the SCB (−) subgroup ($P < 0.0001$) and a higher number of concomitant AEDs at Baseline ($P < 0.0001$). They also had a numerically higher focal seizure frequency at Baseline ($P = 0.0862$; Table 1).

The mean lacosamide treatment duration was 174.1 days (standard deviation [SD] 67.8; median 188.0) with an overall exposure of 148.2 patient-years. The mean lacosamide treatment duration was 180.7 days (SD 71.0; median 189.0) for the SCB (−) subgroup compared to 167.3 days (SD 63.8; median 186.0) for the SCB (+) subgroup. The median modal lacosamide dose during the study was 200 mg/d (range: 50, 600) in the overall population and the SCB (+) and SCB (−) subgroups.

3.2 | Overall population

3.2.1 | Change in AED drug load

In the FAS, the observed ratio of daily dose of concomitant AEDs (excluding lacosamide) to the DDD decreased from Baseline to the end of the Observation period (absolute change: −0.28 [SD 0.64]; mean percentage change: −9.6% [SD 51.1]; Table 2). In the mFAS, the mean percentage change was −8.7% (SD 26.1). The mean percentage changes in patients aged <65 years and ≥65 years (FAS) were −10.5% (SD 55.0; n = 245) and −6.0% (SD 28.3; n = 57), respectively. In patients with epilepsy duration of <10 years and ≥10 years, the mean percentage changes were −8.1% (SD 29.5; n = 151) and −11.3% (SD 66.2; n = 150), respectively.

The observed ratio of daily dose of all AEDs (including addition of lacosamide) to the DDD increased by 15.5% (SD 33.6) from 2.22 (SD 1.02) at Baseline to 2.44 (SD 1.05) by the end of the Observation period (Table 2).

In patients taking one concomitant AED at Baseline, there was no change in the mean ratio of concomitant AED dose to DDD (Figure 2). Decreases in the mean ratio of concomitant AED dose to DDD were observed in patients who were treated with two or more concomitant AEDs at Baseline (Figure 2).

TABLE 1 Patient demographics and epilepsy characteristics (SS)

	SCB (+) (n = 153)	SCB (−) (n = 158)	All patients (N = 311)
Baseline demographics and epilepsy characteristics			
Age, y			
Mean (SD)	44.0 (16.4)	52.5 (16.0)	48.3 (16.7)
Median (range)	43.0 (18, 82)	53.0 (19, 87)	49.0 (18, 87)
<65 y, n (%)	136 (88.9)	117 (74.1)	253 (81.4)
≥65 y, n (%)	17 (11.1)	41 (25.9)	58 (18.6)
Gender			
Male, n (%)	74 (48.4)	92 (58.2)	166 (53.4)
Time since first diagnosis, y			
Median (range)	13.0 (0, 69)	5.0 (0, 61)	9.0 (0, 69)
P-value[a]	<0.0001		
<10 y, n (%)	56 (36.6)	99 (62.7)	155 (49.8)
≥10 y, n (%)	96 (62.7)	58 (36.7)	154 (49.5)
Missing	1 (0.7)	1 (0.6)	2 (0.6)
Baseline focal seizure frequency per 28 d			
Median (range)	2.33 (0.3, 270.0)	1.67 (0.3, 90.0)	2.00 (0.3, 270.0)
P-value[a]	0.0862		
Number of concomitant AEDs at Baseline, n (%)			
0	0	3 (1.9)	3 (1.0)
1	63 (41.2)	127 (80.4)	190 (61.1)
2	71 (46.4)	26 (16.5)	97 (31.2)
≥3	19 (12.4)	2 (1.3)	21 (6.8)
P-value[b]	<0.0001		
Baseline concomitant AEDs, n (%)			
Levetiracetam only	0	101 (63.9)	101 (32.5)
Lamotrigine, carbamazepine, or oxcarbazepine only	61 (39.9)	0	61 (19.6)
Other	92 (60.1)	54 (34.2)	146 (46.9)
None	0	3 (1.9)	3 (1.0)

Abbreviations: AED, antiepileptic drug; SCB, sodium channel–blocking AED; SD, standard deviation; SS, safety set.
[a]Comparison between SCB (+) and SCB (−) subgroups based on Wilcoxon rank-sum test.
[b]Comparison between SCB (+) and SCB (−) subgroups based on Cochran-Mantel-Haenszel test.

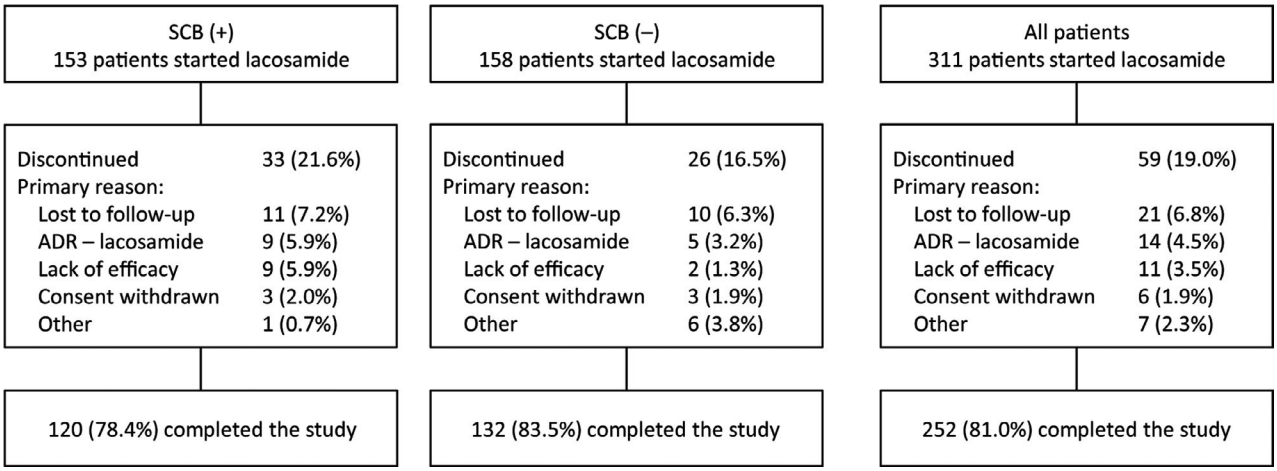

FIGURE 1 Patient disposition by AED use at Baseline (SS). ADR, adverse drug reaction; AED, antiepileptic drug; SCB, sodium channel–blocking AED; SS, safety set

A greater percentage of patients were receiving one concomitant AED at the end of the Observation period compared with Baseline (68.5% vs 61.6%, respectively). Nine patients (3.0%) were receiving lacosamide monotherapy at the end of the Observation period. At the end of the Observation period, the proportion of patients in the FAS taking the following AEDs had changed by ≥1% from Baseline: lamotrigine (−5.3%), valproate (−3.0%), levetiracetam (−2.6%), carbamazepine (−2.6%), clobazam (−2.6%), and topiramate (−1.3%).

3.2.2 | Change in focal seizure frequency

The median percentage reduction in focal seizure frequency per 28 days from Baseline was −53.59% (range: −100.0, 3718.2) at Visit 2 (weeks 2-6), −100.00% (−100.0, 2300.0) at Visit 3 (month 3), and −100.00% (−100.0, 2275.8) at the end of the Observation period in the mFAS (Figure 3A). Of 240 patients in the mFAS, 169 patients (70.4%) achieved a ≥50% reduction in focal seizure frequency per 28 days over the Observation period, and 148 patients (61.7%) achieved a ≥75% reduction. A total of 122 patients (50.8%) achieved seizure freedom (Figure 3D). There were no noteworthy differences in effectiveness with the FAS (data not shown).

3.2.3 | Safety

Sixty-two patients (19.9%) reported 134 AEs. Overall, 57 patients (18.3%) reported ADRs (Table 3). The most commonly reported ADRs (≥1% of patients) were dose >400 mg/d (7.1%), drug ineffective (3.5%), dizziness (2.3%), headache (1.9%), fatigue (1.3%), and nausea, diplopia, and seizure (1.0% each). Adverse drug reactions leading to discontinuation of lacosamide were reported by 17 patients (5.5%), most commonly headache (1.9%), dizziness (1.6%), drug ineffective (1.3%), and seizure (1.0%). Serious ADRs were reported by seven patients (2.3%). No serious ADR was reported by more than one patient.

Two deaths were recorded during the study period. One death, of a 63-year-old man in the SCB (−) group, was because of generalized seizure and malignant brain tumor (glioblastoma). The glioblastoma (grade IV) was present at study entry. The other death, of a 77-year-old man in the SCB (−) group, was because of aspiration pneumonia. There was prolonged immobilization before death. Neither death was considered to be related to lacosamide.

One patient became pregnant during the study period while receiving lacosamide and levetiracetam. Lacosamide was discontinued a few weeks after the pregnancy was reported and it was unknown whether treatment with levetiracetam was continued. The baby was born prematurely (32 weeks, 2 days) but this was not considered to be related to lacosamide.

3.3 | Lacosamide in combination with SCB (+) AEDs

3.3.1 | Change in AED drug load

In patients on concomitant SCB (+) AEDs (FAS), the ratio of concomitant AED dose to DDD decreased from Baseline to the end of the Observation period, while the observed ratio of daily dose of all AEDs (including addition of lacosamide) to the DDD increased (Table 2). The mean percentage changes of concomitant AED dose in patients aged <65 and ≥65 years were −15.9% (SD 68.6; n = 132) and −8.6% (SD 17.3; n = 17), respectively. In patients with epilepsy duration of <10 years, the mean percentage change was −16.8% (SD 29.4; n = 55) compared with −14.2% (SD 79.0; n = 93) in patients with an epilepsy duration of ≥10 years.

TABLE 2 Change in ratio of dose and DDD for the drug load (FAS)

	Ratio of concomitant AED doses (not including lacosamide) and DDD	Ratio of all AED doses (including lacosamide) and DDD
All patients (N = 302)		
Baseline		
Mean (SD)	1.85 (1.08)	2.22 (1.02)
Median (range)	1.67 (<0.1, 6.5)	2.00 (0.4, 6.7)
End of Observation period		
Mean (SD)	1.57 (0.95)	2.44 (1.05)
Median (range)	1.33 (0.0, 4.8)	2.33 (<0.1, 5.9)
Absolute change from Baseline to end of Observation period		
Mean (SD)	−0.28 (0.64)	0.22 (0.61)
Median (range)	0.00 (−3.0, 3.0)	0.33 (−2.2, 3.2)
Percent change from Baseline to end of Observation period		
Mean (SD)	−9.6 (51.1)	15.5 (33.6)
Median (range)	0.0 (−100, 700)	12.5 (−95, 158)
SCB (+) group (n = 149)		
Baseline		
Mean (SD)	2.07 (1.28)	2.40 (1.20)
Median (range)	1.83 (0.2, 6.5)	2.17 (0.7, 6.7)
End of Observation period		
Mean (SD)	1.61 (1.07)	2.51 (1.19)
Median (range)	1.33 (0.0, 4.5)	2.30 (0.2, 5.9)
Absolute change from Baseline to end of Observation period		
Mean (SD)	−0.46 (0.68)	0.11 (0.59)
Median (range)	−0.30 (−3.0, 1.2)	0.17 (−2.2, 1.7)
Percent change from Baseline to end of Observation period		
Mean (SD)	−15.0 (64.8)	10.7 (32.5)
Median (range)	−11.8 (−100, 700)	5.9 (−93, 140)
SCB (−) group (n = 153)		
Baseline		
Mean (SD)	1.64 (0.79)	2.04 (0.78)
Median (range)	1.33 (<0.1, 5.4)	2.00 (0.4, 5.5)
End of Observation period		
Mean (SD)	1.53 (0.81)	2.37 (0.89)
Median (range)	1.33 (0.0, 4.8)	2.33 (<0.1, 5.3)
Absolute change from Baseline to end of Observation period		
Mean (SD)	−0.11 (0.55)	0.33 (0.60)
Median (range)	0.00 (−2.1, 3.0)	0.33 (−1.8, 3.2)
Percent change from Baseline to end of Observation period		
Mean (SD)	−4.4 (31.9)	20.2 (34.1)
Median (range)	0.0 (−100, 164)	20.0 (−95, 158)

Abbreviations: AED, antiepileptic drug; DDD, defined daily dose; FAS, full analysis set; SD, standard deviation.

There was no change in the mean ratio of concomitant AED dose to DDD in patients taking one concomitant AED at Baseline (Figure 2). Decreases were observed in patients receiving two or more concomitant AEDs at Baseline (Figure 2). The proportion of patients receiving one concomitant AED at the end of the Observation period was 54.4%

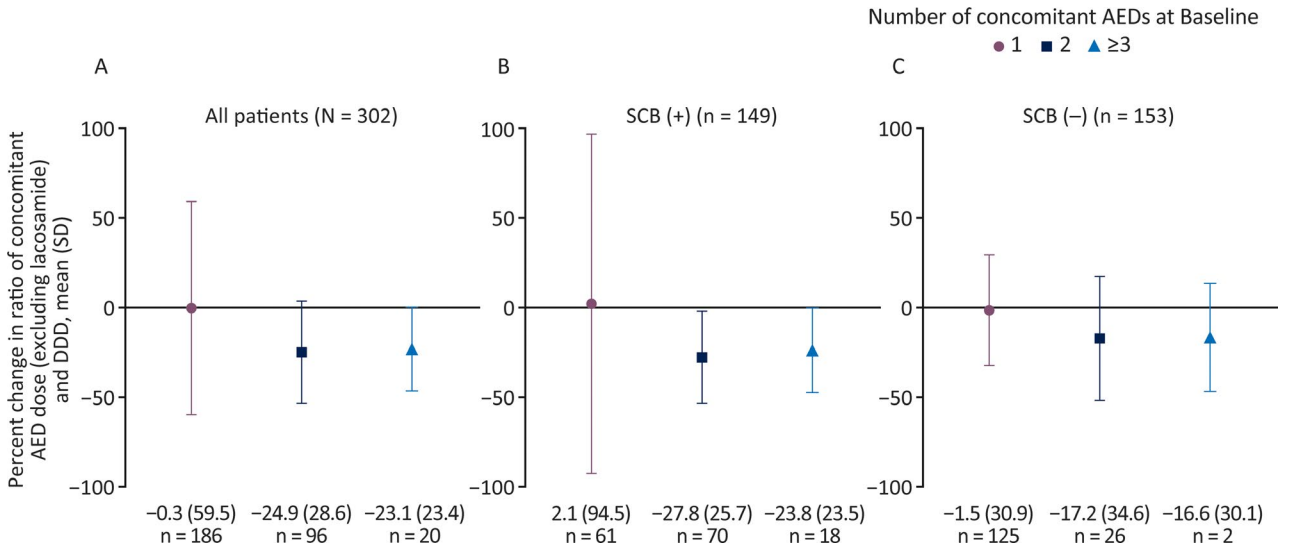

FIGURE 2 Percent change in ratio of concomitant AED dose (not including lacosamide) and DDD from Baseline to the end of the Observation period by number of Baseline AEDs (FAS). (A) All patients; (B) patients on concomitant SCB (+) AEDs; (C) patients on concomitant SCB (−) AEDs. AED, antiepileptic drug; DDD, defined daily dose; FAS, full analysis set; SCB, sodium channel–blocking AED; SD, standard deviation

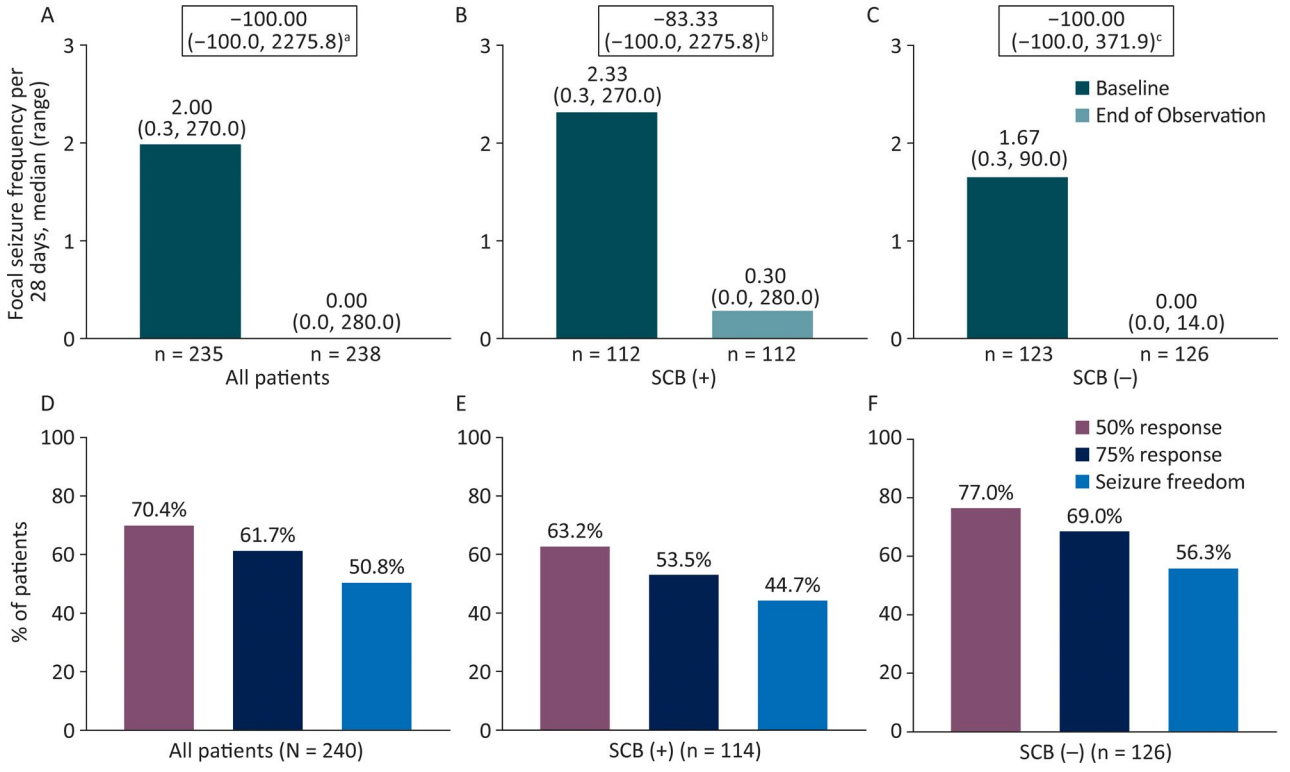

FIGURE 3 Analysis of focal seizure frequency (mFAS). (A–C) Focal seizure frequency per 28 days at Baseline and end of Observation period. Boxes above bars indicate percentage change from Baseline to end of Observation period. (D–F) Proportion of patients with a ≥50% or ≥75% reduction in focal seizure frequency per 28 days from Baseline to the end of the Observation period and proportion of patients who achieved seizure freedom at end of Observation period. (A, D) All patients; (B, E) patients on concomitant SCB (+) AEDs; (C, F) patients on concomitant SCB (−) AEDs. mFAS, modified full analysis set; SCB, sodium channel–blocking antiepileptic drug; SD, standard deviation. [a]n = 234; [b]n = 111; [c]n = 123

TABLE 3 Incidence of adverse drug reactions (SS)

	SCB (+) (n = 153)	SCB (−) (n = 158)	All patients (N = 311)
Number of patients reporting adverse drug reactions, n (%)			
Any	35 (22.9)	22 (13.9)	57 (18.3)
Most common adverse drug reactions[a] (≥1% of patients in any group), n (%)			
Dose >400 mg/d	15 (9.8)	7 (4.4)	22 (7.1)
Drug ineffective	9 (5.9)	2 (1.3)	11 (3.5)
Dizziness	4 (2.6)	3 (1.9)	7 (2.3)
Headache	3 (2.0)	3 (1.9)	6 (1.9)
Fatigue	1 (0.7)	3 (1.9)	4 (1.3)
Nausea	3 (2.0)	0	3 (1.0)
Diplopia	1 (0.7)	2 (1.3)	3 (1.0)
Seizure	1 (0.7)	2 (1.3)	3 (1.0)
Upper abdominal pain	0	2 (1.3)	2 (0.6)
Gastric disorder	0	2 (1.3)	2 (0.6)
Atrioventricular block first degree	0	2 (1.3)	2 (0.6)
Adverse drug reactions leading to discontinuation from the study, n (%)			
Any	11 (7.2)	6 (3.8)	17 (5.5)
Serious adverse drug reactions, n (%)			
Any	1 (0.7)	6 (3.8)	7 (2.3)
Deaths, n (%)			
Any cause	0	2 (1.3)	2 (0.6)

Abbreviations: AED, antiepileptic drug; MedDRA, Medical Dictionary for Regulatory Activities; SS, safety set; SCB, sodium channel–blocking AED.
[a]Preferred Term (MedDRA, version 18.0).

compared with 40.9% at Baseline. Five patients (3.4%) withdrew all concomitant AEDs and were receiving lacosamide monotherapy at the end of the Observation period.

3.3.2 | Change in focal seizure frequency

The median percentage reduction in the number of focal seizures per 28 days in the mFAS from Baseline to the end of the Observation period was −83.33% (Figure 3B). Of 114 patients in the mFAS, 72 (63.2%) and 61 (53.5%) patients achieved a ≥50% and 75% reduction in focal seizure frequency per 28 days over the Observation period, respectively. A total of 51 patients (44.7%) became seizure-free (Figure 3E).

3.3.3 | Safety

Adverse drug reactions were reported by 35 patients (22.9%; Table 3). Eleven patients (7.2%) discontinued treatment because of ADRs, most commonly drug ineffective (2.6%), headache (2.0%), dizziness (2.0%), and nausea (1.3%). Serious ADRs were reported by one patient (0.7%; suicidal ideation).

3.4 | Lacosamide in combination with SCB (−) AEDs

3.4.1 | Change in AED drug load

In patients on concomitant SCB (−) AEDs (FAS), the ratio of concomitant AED dose to DDD decreased from Baseline to the end of the Observation period, while the observed ratio of daily dose of all AEDs (including addition of lacosamide) to the DDD increased (Table 2). In patients aged <65 years, the mean percentage change of concomitant AED dose was −4.2% (SD 32.0; n = 113) compared with −4.9% (SD 31.9; n = 40) in patients aged ≥65 years. In patients with epilepsy duration of <10 years and ≥10 years, the mean percentage changes were −3.1% (SD 28.6; n = 96) and −6.5% (SD 37.0; n = 57), respectively.

There was no change in the mean ratio of concomitant AED dose to DDD in patients taking one concomitant AED at Baseline (Figure 2). Decreases were observed in patients who were receiving two or more concomitant AEDs at Baseline (Figure 2). There were small decreases (≥1%) in concomitant use of valproate (−3.9%), clobazam (−3.3%), and levetiracetam (−1.3%) from Baseline to the end of the Observation period. Four patients (2.6%) withdrew all concomitant AEDs and were receiving lacosamide monotherapy at the end of the Observation period.

3.4.2 | Change in focal seizure frequency

Median percentage reduction in seizure frequency per 28 days in the mFAS from Baseline to the end of the Observation period was −100.00% (Figure 3C). Of 126 patients in the mFAS, 97 (77.0%) and 87 (69.0%) patients achieved a ≥50% and 75% reduction in focal seizure frequency per 28 days over the Observation period, respectively. A total of 71 patients (56.3%) became seizure-free (Figure 3F).

3.4.3 | Safety

Adverse drug reactions were reported by 22 patients (13.9%; Table 3). Six patients (3.8%) discontinued lacosamide because of ADRs, most commonly headache (1.9%), dizziness, seizure, fatigue, and upper abdominal pain (1.3% each). Serious ADRs were reported by six patients (3.8%).

4 | DISCUSSION

In this noninterventional, observational study of adjunctive lacosamide during routine clinical practice in centers in Germany

and Austria, concomitant AED drug load was reduced following introduction of adjunctive lacosamide. Reductions in concomitant AED drug load were observed in patients on concomitant SCB (+) AEDs and in those on SCB (−) AEDs only.

The overall drug load of all AEDs increased as may be expected given the addition of lacosamide; however, dosages of concomitant AEDs and the number of patients receiving combinations of two or three concomitant AEDs were reduced. These observations were seen in the overall population as well as in patients who only received lacosamide doses ≤400 mg/d (mFAS).

While partially compensated by a decrease of the concomitant AED drug load, the overall increased drug load after addition of lacosamide resulted in improvements in seizure control, with the majority of patients (70.4%) achieving a ≥50% reduction in seizure frequency, and half of patients (50.8%) achieving seizure freedom. When indirectly comparing with other observational studies, effectiveness of lacosamide in our study was similar to that observed in another noninterventional study of lacosamide in Germany (≥50% reduction in seizure frequency: 72.5%; seizure freedom: 45.5%).[15] Effectiveness in our study was also comparable to that seen in another noninterventional study of lacosamide in Spain (6-month data: ≥50% reduction in seizure frequency: 76.5%; seizure freedom: 43.9%).[16]

Reductions in concomitant AED drug loads were considerably higher in patients aged <65 years compared with those aged ≥65 years; however, interpretation of this subgroup analysis is limited by the low number of patients aged ≥65 years and the fact that the majority of these were receiving concomitant SCB (−) AEDs and had less severe epilepsy compared with those aged <65 years. Furthermore, patients aged <65 years had a higher drug load and a higher number of concomitant AEDs at Baseline than those aged ≥65 years. Reductions in concomitant AED drug loads were also higher in patients with longer time since diagnosis. However, it should be noted that patients with long-standing diagnosis (≥10 years) also had higher drug load at Baseline.

This study defined two subgroups based on patients' concomitant use of SCB (+) or SCB (−) AEDs at Baseline. Patients in the SCB (+) subgroup had a longer time since diagnosis, higher focal seizure frequency, and a higher number of concomitant AEDs than those in the SCB (−) group, indicating that they were more likely to have severe/uncontrolled epilepsy. The use of an SCB (+) AED regimen in patients with more severe epilepsy is supported by a small study, which suggested that patients with high seizure frequency before treatment initiation were more likely to achieve seizure freedom with SCB (+) AEDs than levetiracetam.[17] Patients in the SCB (+) subgroup also had a higher overall drug load than patients in the SCB (−) subgroup. Given these differences in Baseline characteristics, a direct comparison of study outcomes by mechanism of action of the patient's concomitant AED regimen would not be meaningful. Nevertheless, decreases of concomitant AED drug load tended to be larger in patients with two or more concomitant AEDs including SCB (+) AEDs than in patients with SCB (−) AEDs only. In both the overall population and the AED subgroups, there were no substantial changes in concomitant AED drug load among patients taking lacosamide with only one concomitant AED. Despite the observed Baseline differences, it is apparent that the benefits of lacosamide in terms of seizure reduction and favorable tolerability can be observed in patients receiving both SCB (+) and SCB (−) AEDs. This is consistent with the results of another study using flexible dosing of lacosamide and concomitant AEDs[18] and an audit of lacosamide use in clinical practice.[19]

Higher drug loads have been associated with poorer tolerability and higher incidence of AEs. In a review of 261 adult patients with epilepsy and osteoporosis, cumulative AED drug load was associated with a higher occurrence of fractures.[20] Similarly, a retrospective analysis of patients with epilepsy found poorer cognitive function was more strongly associated with higher number of concomitant AEDs compared with higher DDD.[21] However, in a large study of 809 patients with refractory epilepsy by Canevini et al,[14] incidence of AEs did not differ between monotherapy and polytherapy patients, and did not correlate with AED load. While there were some methodological issues with the assessment of the relationship between tolerability and AED load, Canevini and colleagues suggest that the lack of difference in tolerability between monotherapy and polytherapy treatment regimens may be because of individualization of patients' treatment to optimize efficacy and tolerability. In addition, drug load may not represent an accurate measure of drug exposure because of the effects of physiologic factors (eg, genetic factors influencing liver enzymes and drug-transporter mechanisms; age), comorbidities (eg, hepatic and renal disease and various illnesses changing pharmacokinetics), and interactions with concomitant medications.[14,22]

This noninterventional study aimed to investigate the use of adjunctive lacosamide in routine clinical practice. Few eligibility criteria were defined in order to ensure that enrolled patients were reflective of the wider epilepsy population. Patients participating in the study were taking a variety of different AEDs, different numbers of AEDs, and different dosages. This likely contributed to the observed high variability in the drug load outcomes. Comparison between results in the SCB (+) and SCB (−) groups should be made with caution because of the differences in Baseline characteristics suggesting different patient populations; therefore, no statistical tests were performed. Interpretation of the change in drug load by number of Baseline AEDs is limited by the low numbers of patients taking three or more AEDs at Baseline. Interpretation of the results is also limited by the open-label study design and lack of a direct comparator group given the real-life setting,

and a follow-up limited to 6 months. Furthermore, observed drug load changes are descriptive and the reasons for changing the dose of concomitant AEDs were not documented. Therefore, it was not possible to determine whether reductions in concomitant AEDs were primarily because of improved seizure control with the addition of lacosamide, tolerability considerations, or other reasons. Despite these limitations, this study reflects the use of adjunctive lacosamide and currently available concomitant AEDs in Germany and Austria.

5 | CONCLUSION

In conclusion, while adding lacosamide to an existing AED treatment regimen increased the overall drug load, part of this increase was compensated by a reduction of the concomitant AED drug load, regardless of whether the treatment regimen consisted of SCB (+) or SCB (−) AEDs. Addition of lacosamide resulted in good effectiveness and tolerability. The results of this study indicate that addition of lacosamide in patients with focal seizures could allow clinicians to reduce concomitant AED drug load by withdrawing or reducing the doses of less well-tolerated or less effective AEDs.

ACKNOWLEDGMENTS

The authors thank the patients and their caregivers in addition to the investigators and their teams who contributed to this study. The authors acknowledge Michaela Fuchs, PhD, CMPP (Evidence Scientific Solutions, Horsham, UK) for writing assistance, which was funded by UCB Pharma, and Suzannah Ryan (UCB Pharma, Dublin, Ireland) and Virginie Goffaux, DVM (UCB Pharma, Brussels, Belgium) for manuscript coordination.

CONFLICTS OF INTEREST

This study was funded by UCB Pharma. The authors employed by UCB Pharma were involved in conduct of the research; in study design; in the collection, analysis, and interpretation of data; in writing the report; and preparation of the article and the decision to submit the article for publication. Fritjof Reinhardt and Yvonne Weber report no conflicts of interest. Thomas Mayer has been a consultant for, and/or received honoraria for presentations from UCB Pharma, Desitin, Eisai, Bial, and GW Pharmaceuticals. Gerhard Luef has been a consultant for, and/or received honoraria for presentations from Eisai, Novartis, Sage Therapeutics, and UCB Pharma. Lars Joeres, Frank Tennigkeit, Marc De Backer, and Tanja Webers are employees of UCB Pharma. Scarlett Hellot is contracted by UCB Pharma for statistical services. Peter Dedeken and Thomas Lauterbach were employees of UCB Pharma at the time of the study. Stephan Arnold has been a consultant for, and/or received honoraria for presentations from Bial, Desitin, Eisai, UCB Pharma, and Upsher-Smith. Qualified researchers whose proposed use of the data has been approved by an independent review panel will be given access to anonymized individual participant data and redacted study documents. Additional information is available at www.clinicalstudydatarequest.com. 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.

CO-INVESTIGATOR APPENDIX

The authors acknowledge the SP1065 study investigators for their contributions to data acquisition: Susanne Asenbaum-Nan (Landesklinikum Amstetten, Neurologie, Amstetten, Austria); Stephan Behrens (Praxis Dr. med. Stephan Behrens, Jülich, Germany); Florian Bethke (Klinikum Ibbenbüren, Klinik für Neurologie, Ibbenbüren, Germany); Monika Bös (Medizinisches Versorgungszentrum Sieglar GmbH, Neurologie, Troisdorf, Germany); Ulrike Bongartz (Neurologische Praxis, Köln, Germany); Angelika Christopher (Praxis Dr. med. Angelika Christopher, Berlin, Germany); Christian Geber (Universitätsmedizin Mainz, Klinik und Poliklinik für Neurologie, Mainz, Germany); Frank Halbgewachs (Neurologische Praxis Heidenheim, Heidenheim, Germany); Hajo Hamer (Universitätsklinikum Erlangen, Erlangen, Germany); Frank Hoffman (Krankenhaus Martha-Maria Halle Dölau gGmbH, Halle [Saale], Germany); Andreas Hufnagel (Neuro-Consil GmbH, Düsseldorf, Germany); Oliver Kastrup (Universitätsklinikum Essen, Klinik für Neurologie, Essen, Germany); Christoph Kellinghaus (Klinikum Osnabrück GmbH, Klinik für Neurologie, Osnabrück, Germany); Irene Klyk (Praxis Dr. med. Irene Klyk, Rüsselsheim, Germany); Andreas Kowalik (Neurologische Praxis Dr. Kowalik, Stuttgart, Germany); Frank Kühn (Praxis Dr. med. Frank Kühn, Oranienburg, Germany); Borries Kukowski (Praxis Dr. Kukowski, Göttingen, Germany); Albrecht Kunze (Friedrich-Schiller-Universität, Klinik für Neurologie, Jena, Germany); Michael Lang (Nervenfachärztliche Gemeinschaftspraxis Ulm, Ulm, Germany); Nicolas Lang (Universitätsklinikum Schleswig-Holstein, Neurologische Klinik, Kiel, Germany); Florian-Philip Losch (Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Abteilung für Neurologie, Berlin, Germany); Ulrike Niedermüller (Krankenhaus Barmherzigen Schwestern Ried, Neurologie, Ried, Austria); Michael Nitsche (Universitätsklinikum Göttingen, Neurologische Klinik, Göttingen, Germany); Michael Rademacher (Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany); Gernot Reimann (Klinikum Dortmund gGmbH, Dortmund, Germany); Stefan Ries (Neuro Centrum Science GmbH, Erbach, Germany); Brigitte Scheid (Praxis Dr. Scheid, Leipzig, Germany); Friedhelm Schmitt

(Klinik der Otto-Von-Guericke-Universität Magdeburg, Universitätsklinik für Neurologie, Magdeburg, Germany); Bettina Schmitz (Vivantes Humboldt Klinikum, Klinik für Neurologie, Berlin, Germany); Erich Scholz (Neurologische Praxis, Böblingen, Germany); Johannes Schwarz (Klinik Haag, Haag, Germany); Joachim Springub (Praxis für Neurologie und Psychiatrie, Westerstede, Germany); Bernhard Steinhoff (Epilepsiezentrum Kork, Kehl-Kork, Germany); Jens Tröger (Praxisgemeinschaft Tröger, Mittweida, Germany); Florian Weißinger (Charité Universitätsmedizin Berlin, Klinik für Neurologie, Berlin, Germany); Angelika Wirbatz (Universitätsklinikum Gießen und Marburg GmbH, Standort Gießen, Medizinisches Zentrum für Neurologie und Neurochirurgie, Gießen, Germany); and Kai Wohlfarth (Berufsgenossenschaftliche Kliniken, Akademisches Lehrkrankenhaus Bergmanntrost, Klinik für Neurochirurgie, Halle, Germany).

REFERENCES

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–319.
2. Malerba A, Ciampa C, De Fazio S, Fattore C, Frassine B, La Neve A, et al. Patterns of prescription of antiepileptic drugs in patients with refractory epilepsy at tertiary referral centres in Italy. Epilepsy Res. 2010;91:273–282.
3. St Louis EK, Rosenfeld WE, Bramley T. Antiepileptic drug monotherapy: the initial approach in epilepsy management. Curr Neuropharmacol. 2009;7:77–82.
4. Perucca E, Beghi E, Dulac O, Shorvon S, Tomson T. Assessing risk to benefit ratio in antiepileptic drug therapy. Epilepsy Res. 2000;41:107–139.
5. Foldvary-Schaefer N, Fong JS, Morrison S, Wang L, Bena J. Lacosamide tolerability in adult patients with partial-onset seizures: impact of planned reduction and mechanism of action of concomitant antiepileptic drugs. Epilepsy Behav. 2016;57:155–160.
6. Deckers CLP, Hekster YA, Keyser A, Van Lier HJJ, Meinardi H, Renier WO. Monotherapy versus polytherapy for epilepsy: a multicenter double-blind randomized study. Epilepsia. 2001;42:1387–1394.
7. Millul A, Iudice A, Adami M, Porzio R, Mattana F, Beghi E. Alternative monotherapy or add-on therapy in patients with epilepsy whose seizures do not respond to the first monotherapy: an Italian multicenter prospective observational study. Epilepsy Behav. 2013;28:494–500.
8. Semah F, Thomas P, Coulbaut S, Derambure P. Early add-on treatment vs alternative monotherapy in patients with partial epilepsy. Epileptic Disord. 2014;16:165–174.
9. Deckers CLP, Hekster YA, Keyser A, Meinardi H, Renier WO. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. Epilepsia. 1997;38:570–575.
10. Rogawski MA, Tofighy A, White HS, Matagne A, Wolff C. Current understanding of the mechanism of action of the antiepileptic drug lacosamide. Epilepsy Res. 2015;110:189–205.
11. Vimpat® (lacosamide) summary of product characteristics. Brussels, Belgium: UCB Pharma, SA; 2018. https://www.ema.europa.eu/documents/product-information/vimpat-epar-product-information_en.pdf. Accessed April 29, 2019.
12. Vimpat® (lacosamide) C-V prescribing information. Smyrna, GA: UCB, Inc.; 2019. https://www.vimpat.com/vimpat-prescribing-information.pdf. Accessed April 29, 2019.
13. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2013. Oslo; 2012. https://www.whocc.no/filearchive/publications/1_2013guidelines.pdf. Accessed April 29, 2019.
14. Canevini MP, De Sarro G, Galimberti CA, Gatti G, Licchetta L, Malerba A, et al. Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. Epilepsia. 2010;51:797–804.
15. Runge U, Arnold S, Brandt C, Reinhardt F, Kühn F, Isensee K, et al. A noninterventional study evaluating the effectiveness and safety of lacosamide added to monotherapy in patients with epilepsy with partial-onset seizures in daily clinical practice: The VITOBA study. Epilepsia. 2015;56:1921–1930.
16. Villanueva V, Garcés M, López-Gomáriz E, Serratosa JM, González-Giráldez B, Parra J, et al. Early add-on lacosamide in a real-life setting: results of the REALLY study. Clin Drug Investig. 2015;35:121–131.
17. Lloyd-Smith AJ, Hennessy R, Hegde M, Gidal BE, French JA. Comparison of levetiracetam versus sodium channel blockers as first line antiepileptic drug in participants with high seizure burden using Human Epilepsy project data. AES 2016 Annual Meeting Abstract Database AESnet.org Abs 2.103.
18. Baulac M, Coulbaut S, Doty P, McShea C, De Backer M, Bartolomei F, et al. Adjunctive lacosamide for focal epilepsy: an open-label trial evaluating the impact of flexible titration and dosing on safety and seizure outcomes. Epileptic Disord. 2017;19:186–194.
19. Stephen LJ, Kelly K, Parker P, Brodie MJ. Adjunctive lacosamide – 5 years' clinical experience. Epilepsy Res. 2014;108:1385–1391.
20. Beerhorst K, Schouwenaars FM, Tan IY, Aldenkamp AP. Epilepsy: fractures and the role of cumulative antiepileptic drug load. Acta Neurol Scand. 2012;125:54–59.
21. Witt JA, Elger CE, Helmstaedter C. Adverse cognitive effects of antiepileptic pharmacotherapy: each additional drug matters. Eur Neuropsychopharmacol. 2015;25:1954–1959.
22. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs–best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring. ILAE commission on therapeutic strategies. Epilepsia. 2008;49:1239–1276.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Reinhardt F, Weber YG, Mayer T, et al. Changes in drug load during lacosamide combination therapy: A noninterventional, observational study in German and Austrian clinical practice. *Epilepsia Open*. 2019;4:409–419. https://doi.org/10.1002/epi4.12346