



Lacosamide in patients with epilepsy of cerebrovascular etiology

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Objectives: To assess tolerability and efficacy of lacosamide in adults with cerebrovascular epilepsy etiology (CVEE).

Materials and methods: Exploratory *post hoc* analyses of a double-blind, initial monotherapy trial of lacosamide vs carbamazepine-controlled release (carbamazepine-CR) (SP0993; NCT01243177); a double-blind conversion to lacosamide monotherapy trial (SP0902; NCT00520741); and an observational study of adjunctive lacosamide added to one antiepileptic drug (SP0973 VITOBA; NCT01098162). Patients with CVEE were identified based on epilepsy etiology recorded at baseline.

Results: In the initial monotherapy trial, 61 patients had CVEE (lacosamide: 27; carbamazepine-CR: 34). 20 (74.1%) patients on lacosamide (27 [79.4%] on carbamazepine-CR) reported treatment-emergent adverse events (TEAEs), most commonly ($\geq 10\%$) headache, dizziness, and fatigue (carbamazepine-CR: headache, dizziness). A numerically higher proportion of patients on lacosamide than carbamazepine-CR completed 6 months (22 [81.5%]; 20 [58.8%]) and 12 months (18 [66.7%]; 17 [50.0%]) treatment without seizure at last evaluated dose. In the conversion to monotherapy trial, 26/30 (86.7%) patients with CVEE reported TEAEs, most commonly (≥ 4 patients) dizziness, convulsion, fatigue, headache, somnolence, and cognitive disorder. During lacosamide monotherapy, 17 (56.7%) patients were 50% responders and six (20.0%) were seizure-free. In the observational study, 36/83 (43.4%) patients with CVEE reported TEAEs, most commonly ($\geq 5\%$) fatigue and dizziness. Effectiveness was assessed for 75 patients. During the last 3 months, 60 (80%) were 50% responders and 42 (56.0%) were seizure-free.

Conclusions: These exploratory *post hoc* analyses suggested lacosamide was generally well tolerated and effective in patients with CVEE, with data from the initial monotherapy trial suggesting numerically better efficacy than carbamazepine-CR.

KEYWORDS

antiepileptic drugs, elderly, epilepsy, lacosamide, seizures, stroke

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1 | INTRODUCTION

Cerebrovascular disease, particularly stroke, is one of the most common causes of new-onset epilepsy among older adults with identified epilepsy etiology.^{1,2} Considerations for the antiepileptic drug (AED) treatment of post-stroke epilepsy include the patient's susceptibility to age-related side effects and potential drug-drug interactions.^{3,4} Treatment with non-enzyme-inducing AEDs may be preferable, as enzyme induction may interfere with secondary stroke prophylaxis and exacerbate vascular risk.³⁻⁵ Few studies have evaluated the tolerability and efficacy of AEDs in post-stroke epilepsy.^{6,7}

Lacosamide is a non-enzyme-inducing AED indicated for monotherapy and adjunctive therapy of focal (partial-onset) seizures in patients 4 years of age and older in the United States,⁸ the European Union,⁹ and several other countries (prescribing regulations vary). Preclinical *in vitro*¹⁰ and *in vivo*^{11,12} models of ischemia or ischemic stroke have suggested neuroprotective effects of lacosamide. A small-scale pilot study ($n = 16$) indicated that intravenous lacosamide had a favorable tolerability and efficacy profile when used as initial treatment for post-stroke non-convulsive status epilepticus in elderly patients.¹³

These exploratory *post hoc* analyses were conducted to assess the tolerability and efficacy of oral lacosamide in adults with cerebrovascular epilepsy etiology (CVEE).

2 | MATERIALS AND METHODS

Post hoc analyses were conducted on data collected in three trials: a double-blind, non-inferiority, initial monotherapy trial of lacosamide vs carbamazepine-controlled release (carbamazepine-CR) (SP0993; NCT01243177)¹⁴; a historical-controlled double-blind conversion to lacosamide monotherapy trial (SP0902; NCT00520741)¹⁵; and an observational study of adjunctive lacosamide added to one baseline AED (SP0973 VITObA; NCT01098162).¹⁶ Patients with CVEE were selected based on epilepsy etiology data recorded by the investigators at baseline of each trial. Patients with an etiology category of "cerebrovascular accident" (initial monotherapy trial), "vascular causes" (conversion to lacosamide monotherapy trial), or "cerebrovascular etiology" (observational study) were included. Tolerability and efficacy/effectiveness outcomes were analyzed separately for each trial, as detailed below.

The trials were conducted in accordance with Good Clinical Practice requirements, the Declaration of Helsinki and local laws. The protocols were reviewed by institutional and local ethics committees. All patients provided signed informed consent for their participation (double-blind trials) or use of medical data (observational study).

2.1 | Initial monotherapy with lacosamide or carbamazepine-CR

Eligible patients were aged ≥ 16 years with newly/recently diagnosed epilepsy and unprovoked focal or generalized tonic-clonic

seizures (without signs of focal onset) (Table 1). Patients were randomized 1:1 to lacosamide or carbamazepine-CR, with strata defined by seizure-count (≤ 2 or > 2 seizures) in the 3 months prior to screening. Doses were up-titrated over 2 weeks from initial dose (lacosamide, 100 mg/day; carbamazepine-CR: 200 mg/day) to the first target dose level (200 mg/day; 400 mg/day). Flexible up-titration to the second and third target dose levels (lacosamide: 400/600 mg/day; carbamazepine-CR: 800/1200 mg/day) was based on seizure control, an approach closely reflecting clinical practice. Following 1-week stabilization at the first target dose, patients entered a 6-month evaluation period. If a seizure occurred, the dose was escalated to the next target dose level (3-week titration and stabilization) and the 6-month evaluation began again. Patients who experienced a seizure at the third target dose were withdrawn from the trial. Upon completion of the evaluation period, patients continued to a 6-month maintenance period. During evaluation and maintenance, patients on the second and third target doses could undergo one dose reduction if required for tolerability reasons. Patients with a dose reduction could not return to their previous dose and were withdrawn if a new seizure occurred. Patients were eligible to participate in a double-blind extension trial (SP0994; NCT01465997) if they remained seizure-free during maintenance, or experienced a seizure during maintenance while on the first or second target dose levels.

Data were analyzed for the safety set (SS) and full analysis set (FAS); both analysis sets included all randomized patients who received at least one dose of trial medication. Tolerability outcomes included treatment-emergent adverse events (TEAEs) during treatment (titration, stabilization, evaluation, and maintenance) (summarized descriptively). Efficacy outcomes included the Kaplan-Meier estimated proportion of patients remaining seizure-free for 6 and 12 consecutive months following stabilization at last evaluated dose and for 12 consecutive months from the date of first trial dose. Patients who withdrew from the trial without a seizure were censored at the time of withdrawal. Kaplan-Meier estimates were adjusted for number of seizures (≤ 2 or > 2) in the 3 months before screening. Additional efficacy outcomes included the observed proportion of patients who completed 6 and 12 consecutive months of treatment and were seizure-free following the last evaluated dose and from the date of first trial dose.

2.2 | Conversion to lacosamide monotherapy

Eligible patients were aged 16-70 years, on stable doses of one or two AEDs, and were experiencing between two and ≤ 40 partial-onset seizures/28 days during the 8-week prospective baseline (Table 1). If the patient was on two AEDs, the dosage of the second AED was required to be $\leq 50\%$ of the minimum recommended maintenance dose per the United States label. Following baseline, patients were randomized 3:1 to 400 mg/day or 300 mg/day lacosamide. The 300 mg/day arm was included to allow blinding and ensure a trial design consistent with the historical-control studies.

TABLE 1 Trials included in these exploratory *post hoc* analyses

	Initial monotherapy with LCM or CBZ-CR	Conversion to LCM monotherapy	LCM adjunctive to one baseline AED
Study	SP0993	SP0902	SP0973
CT.gov identifier	NCT01243177	NCT00520741	NCT01098162
Phase	Phase 3	Phase 3	Phase 4
Design	Randomized, double-blind, non-inferiority trial	Randomized, double-blind, historical-controlled	Observational; physician's decision to add lacosamide had been reached prior to, and independently of, the decision to include the patient in the study.
Treatment duration	Up to 118 wk (2-wk titration; 1-wk stabilization; 6-mo evaluation; 6-mo maintenance) ^a	Up to 19 wk (3-wk titration; 16-wk maintenance [6-wk Background AED withdrawal and 10-wk LCM monotherapy])	Up to 6 mo
Starting dose	LCM 100 mg/day CBZ-CR 200 mg/day	LCM 200 mg/day	Based on physician discretion
Maintenance	LCM 200-600 mg/day CBZ-CR 400-1200 mg/day	LCM 300 and 400 mg/day	Based on physician discretion
Number of patients (SS)	LCM: 444 CBZ-CR: 442	LCM 300 mg/day: 106 LCM 400 mg/day: 319	SS: 571
Main inclusion criteria			
Age	≥16 y	16-70 y	≥16 y ^b
Seizure type	Newly/recently diagnosed epilepsy with unprovoked partial-onset seizures (with clear focal origin) or generalized tonic-clonic seizures (without clear focal origin)	Diagnosis of epilepsy with simple partial seizures (motor component) and/or complex partial seizures (with or without secondary generalization)	Partial-onset seizures with or without secondary generalization ^b
Baseline seizure frequency	2 unprovoked seizures (separated by ≥48 h) in the previous 12 mo, of which at least one had occurred in the previous 3 mo	At least 2 and ≤40 partial-onset seizures per 28 d during 8-wk prospective baseline period	Physician discretion
Background AEDs at LCM initiation	None ^c	1 or 2 marketed AEDs at a stable dose for at least 28 d before Visit 1 and during baseline (dosage of second AED was ≤50% of minimum recommended maintenance dose per USA label)	1 AED
Main exclusion criteria			
Criteria related to seizure type, disorders, and cardiac comorbidities	<ul style="list-style-type: none"> • Current/previous seizure clusters or status epilepticus • Seizure types other than focal or generalized tonic-clonic seizures (without clear focal origin) • Non-epileptic seizures, conversion disorders, or other non-epileptic events that could have been confused with seizures • Sick sinus syndrome without a pacemaker, second- or third-degree atrioventricular block, or any other clinically significant electrocardiogram abnormalities • Myocardial infarction in the previous 3 mo • New York Heart Association Class III or IV heart failure 	<ul style="list-style-type: none"> • History of status epilepticus within previous year, cluster seizures within 8 wk of study start • History of primary generalized epilepsy or unclassified seizures • Seizure disorder characterized primarily by isolated auras (ie, simple partial seizures without observable motor signs) • Any seizure-free period lasting 28 d or longer during baseline • Sick sinus syndrome without a pacemaker, or second- or third-degree atrioventricular block • Myocardial infarction in the previous 3 mo • New York Heart Association Class III or Class IV heart failure • Conversion disorders or other non-epileptic ictal events 	Not applicable for this study

Abbreviations: AED, antiepileptic drug; CBZ-CR, carbamazepine-controlled release; LCM, lacosamide.

^aIn the SP0993 trial, 6 mo was equivalent to 26 wk.

^bPer therapeutic guidelines and approved indication at the time of the study (SmPC 2008).

^cPatients with AED treatment in the 6 mo before screening were excluded.

Lacosamide was initiated at 200 mg/day and up-titrated over 3 weeks. Upon reaching their randomized dose, patients entered the 16-week lacosamide maintenance period. Background AEDs were withdrawn over 6 weeks followed by a 10-week lacosamide monotherapy period. The primary background AED was tapered in approximately equal decrements every 2 weeks. If the patient was taking two background AEDs, the second AED was withdrawn on day 1 of the AED withdrawal period. A single reduction in lacosamide dose was permitted during maintenance, if required for tolerability reasons.

Tolerability outcomes included TEAEs during treatment (titration and maintenance) and were summarized for the SS (all patients who received at least one lacosamide dose). Efficacy outcomes included 50% and 75% responders (patients with a $\geq 50\%$ or $\geq 75\%$ reduction in seizure frequency/28 days in comparison with baseline) and patients achieving seizure freedom during the 10-week lacosamide monotherapy period. Efficacy outcomes were summarized for the SS and completer set (patients who completed the monotherapy period).

2.3 | Lacosamide as adjunctive therapy to one baseline AED

Patients were consecutively enrolled from specialized epilepsy outpatient units, as well as from hospital-based and office-based neurologists in Germany. The decision to prescribe lacosamide was made by the physician prior to and independently of patient enrollment, according to the indication at the time of the study (adjunctive therapy of focal seizures in patients with epilepsy 16 years of age or older [2008 SmPC]). Eligible patients were receiving treatment with one AED at the time of initiation of lacosamide (Table 1). Dosing was at the physician's discretion, with lacosamide treatment recommended according to the 2008 SmPC. Upon enrollment, patients provided seizure frequency for the 3 months before the first lacosamide dose (retrospective baseline). Data were collected prospectively at routine visits over 6 months, or until discontinuation of lacosamide. A visit was planned for month 3, per usual clinical practice, with a final visit at month 6 or study termination. Seizures were reported per usual clinical practice (spontaneous reporting or patient diary).

Tolerability outcomes included TEAEs. All patients who received at least one lacosamide dose (SS) were included in descriptive analyses of tolerability outcomes. Effectiveness outcomes were 50% and 75% responders (patients with a $\geq 50\%$ or $\geq 75\%$ reduction from baseline in seizure frequency/28 days) and seizure freedom at the final visit (seizure frequency during the 3 months prior to the visit was compared with 3-month retrospective baseline). Effectiveness was analyzed for the FAS (all SS patients with valid baseline and post-baseline seizure frequency data) and the modified FAS (mFAS; FAS patients treated with in-label lacosamide dosages only [up to 400 mg/day]).

3 | RESULTS

3.1 | Initial monotherapy with lacosamide or carbamazepine-CR

Of 886 patients treated in the initial monotherapy trial, 61 (6.9%) had CVEE and were included in the SS/FAS for these analyses (Table 2). Twenty-seven patients were randomized to lacosamide and 34 to carbamazepine-CR. Eighteen (66.7%) patients on lacosamide and 17 (50.0%) on carbamazepine-CR completed the trial. The most common reasons for discontinuation ($\geq 10\%$ of patients) were adverse events (AEs) in patients on lacosamide, and AEs and lack of efficacy in patients on carbamazepine-CR (Table 2). A higher proportion of patients on lacosamide (19 [70.4%]) than carbamazepine-CR (15 [44.1%]) continued to the long-term extension trial.

Baseline demographics were generally comparable between treatment groups, although patients on lacosamide were older (Table 3). Patients on lacosamide had a higher prevalence of comorbid conditions (median: 4.0) than those on carbamazepine-CR (3.0) (Table 3). Six (22.2%) patients on lacosamide and seven (20.6%) on carbamazepine-CR had an ongoing cardiac disorder, most commonly (≥ 2 patients) atrial fibrillation (lacosamide: three [11.1%]; carbamazepine-CR: one [2.9%]) and myocardial ischemia (none; three [8.8%]). Median (Q1, Q3) numbers of seizures in the previous 3 months (lacosamide: 3.0 [2.0, 5.0]; carbamazepine-CR: 3.0 [1.0, 5.0]) and in the past year (4.0 [3.0, 9.0]; 5.0 [2.0, 15.0]) were similar in both treatment groups.

During the treatment period, the median duration of exposure to trial medication was 385 (range: 12, 498) days in the lacosamide group and 381 (6, 574) days in the carbamazepine-CR group. Twenty (74.1%) patients on lacosamide and 19 (55.9%) on carbamazepine-CR had >364 days of treatment. A higher proportion of patients on lacosamide (24 [88.9%]) than carbamazepine-CR (23 [67.6%]) remained on the lowest target dose level. No patients on lacosamide and five (14.7%) on carbamazepine-CR escalated to the highest target dose.

The overall incidence of TEAEs during the treatment period was similar in patients on lacosamide and carbamazepine-CR (Table 4). TEAEs were considered to be drug-related (opinion of the investigator) in eight (29.6%) patients on lacosamide and 17 (50.0%) on carbamazepine-CR. Headache, dizziness, and fatigue were the most common TEAEs ($\geq 10\%$) with lacosamide, and headache and dizziness were most common TEAEs with carbamazepine-CR. Cardiac TEAEs were reported by one (3.7%) patient on lacosamide (first-degree atrioventricular block) and two (5.9%) on carbamazepine-CR (first-degree atrioventricular block and pericardial hemorrhage; one patient each). Fall was reported by two (7.4%) patients on lacosamide and one (2.9%) on carbamazepine-CR. Most TEAEs were mild or moderate in intensity; four (14.8%) patients on lacosamide and four (11.8%) on carbamazepine-CR had a severe TEAE. No specific TEAE (preferred term) was considered to be severe in >1 patient in either group (Table S1).

TABLE 2 Disposition of patients with cerebrovascular epilepsy etiology (SS)

	Initial monotherapy with LCM or CBZ-CR		Conversion to LCM monotherapy	LCM adjunctive to one baseline AED
	CBZ-CR	LCM	LCM	LCM
Received trial medication, n	34	27	30	83 Attended final visit: 82 (100)
Completed, n (%)	17 (50.0)	18 (66.7)	22 (73.3)	Continuing LCM at final visit: 69 (84.1) ^a
Discontinued, n (%)	17 (50.0)	9 (33.3)	8 (26.7)	12 (14.6)
Due to adverse event	7 (20.6)	3 (11.1)	5 (16.7)	7 (8.5)
Protocol violation	2 (5.9)	2 (7.4)	0	0
Consent withdrawn/patient request	1 (2.9)	2 (7.4)	0	5 (6.1)
Due to lack of efficacy	5 (14.7)	1 (3.7)	3 (10.0)	1 (1.2)
Lost to follow-up	2 (5.9)	1 (3.7)	0	1 (1.2)

Abbreviations: CBZ-CR, carbamazepine-controlled release; LCM, lacosamide; SS, safety set.

^aFor one (1.2%) patient, the status of LCM therapy at the final visit (continuing/discontinued) was unknown.

Serious TEAEs were reported by five (18.5%) patients on lacosamide and seven (20.6%) on carbamazepine-CR (Table 4). No specific TEAE (preferred term) was considered to be serious in >1 patient on lacosamide; three (8.8) patients on carbamazepine-CR had serious TEAEs of partial seizures with secondary generalization. Three (11.1%) patients on lacosamide and seven (20.6%) on carbamazepine-CR had a TEAE leading to discontinuation. No TEAEs led to discontinuation in >1 patient in either group (Table S1). One patient in the lacosamide group died because of subarachnoid hemorrhage following a skull fracture (circumstances unknown); this death was not considered to be related to lacosamide.

A numerically higher proportion of patients on lacosamide than carbamazepine-CR completed 6 months (22 [81.5%] vs 20 [58.8%]) and 12 months (18 [66.7%] vs 17 [50.0%]) of treatment without a seizure at the last evaluated dose level (Figure 1A). The stratified Kaplan-Meier estimates for 6- and 12-month seizure freedom at last evaluated dose were 95.5% and 91.1% on lacosamide, and 82.0% and 75.1% on carbamazepine-CR, respectively. Analyses performed from the first trial dose showed 6- and 12-month seizure freedom with lacosamide in 18 (66.7%) and 15 (55.6%) patients, respectively. In the carbamazepine-CR group, 6- and 12-month seizure freedom was observed in 16 (47.1%) and 13 (38.2%) patients, respectively. The stratified Kaplan-Meier estimates for 12-month seizure freedom from the first trial dose were 66.4% on lacosamide and 44.2% on carbamazepine-CR.

3.2 | Conversion to lacosamide monotherapy

Of 425 patients treated with lacosamide in the conversion to monotherapy trial, 30 (7.1%) had CVEE (SS; Table 2). Twenty-three patients were randomized to 400 mg/day lacosamide and seven to 300 mg/day. Overall, 22 (73.3%) patients completed the lacosamide

monotherapy period; one discontinued during titration (due to an AE), five discontinued during the AED withdrawal period (due to lack of efficacy [3] and AEs [2]), and two discontinued during monotherapy (due to AEs).

Patients had a mean age of 42.3 years and a median time since epilepsy diagnosis of 10.3 years (Table 3). The patient population was highly comorbid, with a median of eight ongoing conditions at trial entry; 21 (70.0%) patients reported five or more comorbid conditions (Table 3). One (3.3%) patient had an ongoing cardiac disorder (mitral valve stenosis). On the day of first trial dose, 20 (66.7%) patients were taking one background AED and 10 (33.3%) were taking two background AEDs. Primary background AEDs were levetiracetam (11 [36.7%]), carbamazepine (five [16.7%]), topiramate (four [13.3%]), valproate (four [13.3%]), lamotrigine (two [6.7%]), oxcarbazepine (two [6.7%]), phenytoin (one [3.3%]), and zonisamide (one [3.3%]).

During the treatment period, 26 (86.7%) patients reported a TEAE and 20 (66.7%) reported a TEAE that was considered to be drug-related (Table 4). The most common TEAEs (≥4 patients) were dizziness, convulsion, fatigue, headache, somnolence, and cognitive disorder. The incidences of these TEAEs were higher during lacosamide titration than during the AED withdrawal and lacosamide monotherapy periods, with the exception of TEAEs coded to convulsion (Figure S1). No patients reported convulsion during titration, whereas 3/29 (10.3%) had convulsion during AED withdrawal and 2/24 (8.3%) during monotherapy. Convulsion was the only serious TEAE reported in >1 patient (three [10%]) (Table S1). Two (6.7%) patients reported cardiac TEAEs (acute myocardial infarction [one], palpitations [one], stress cardiomyopathy [one], and tachycardia [one]). No falls were reported. Five (16.7%) patients discontinued due to TEAEs (convulsion: four [13.3%]; pruritus allergy: one [3.3%]).

In the SS (n = 30), 17 (56.7%) patients were 50% responders, 12 (40.0%) were 75% responders, and six (20.0%) were seizurefree

TABLE 3 Baseline demographic and epilepsy characteristics of patients with cerebrovascular epilepsy etiology (SS)

	Initial monotherapy with LCM or CBZ-CR		Conversion to LCM monotherapy	LCM adjunctive to one baseline AED
	CBZ-CR (n = 34)	LCM (n = 27)	LCM (n = 30)	LCM (n = 83)
Patient demographics				
Age, mean (SD), y	54.5 (16.5)	61.4 (11.8)	42.3 (14.5)	62.6 (14.6)
<65, n (%)	22 (64.7)	13 (48.1)	28 (93.3)	36 (43.4)
≥65, n (%)	12 (35.3)	14 (51.9)	2 (6.7)	47 (56.6)
Male, n (%)	23 (67.6)	20 (74.1)	11 (36.7)	41 (49.4)
Epilepsy history				
Age at diagnosis, median (range), y	57.5 (23, 85)	64.0 (37, 79)	30.4 (0.7, 65.8)	58.0 (6, 84)
Time since diagnosis, median (range), y	0.06 (<0.1, 0.9)	0.08 (<0.1, 0.9)	10.3 (0.6, 35.9)	3.0 (0, 54)
Baseline seizure frequency/28 d, median (range)	NA	NA	6.6 (2.0, 30.0)	2.0 (0.0, 26.7)
Classification of seizures ^a				
Partial-onset seizures (focal), n (%)	34 (100)	26 (96.3)	30 (100)	NA
Simple partial (focal aware)	17 (50.0)	9 (33.3)	21 (70.0)	NA
Complex partial (focal impaired awareness)	14 (41.2)	16 (59.3)	28 (93.3)	NA
Partial evolving to secondarily generalized (focal to bilateral tonic-clonic)	16 (47.1)	11 (40.7)	22 (73.3)	NA
Generalized seizures, n (%)				
Tonic-clonic	0	1 (3.7)	0	NA
Number of lifetime AEDs, n (%) ^b				
0	NA	NA	6 (20.0)	0
1	NA	NA	6 (20.0)	51 (61.4)
2	NA	NA	7 (23.3)	14 (16.9)
3+	NA	NA	11 (36.7)	18 (21.7)
Medical history (previous/ongoing medical conditions that occurred before trial entry)				
Any condition, n (%)	34 (100)	27 (100)	29 (96.7)	83 (100.0)
Condition by System Organ Class reported in ≥40% of all patients in any of the three trials, n (%) (numbers meeting this criterion are bolded)				
Nervous system disorders	32 (94.1)	27 (100.0)	28 (93.3)	75 (90.4)
Vascular disorders	23 (67.6)	19 (70.4)	13 (43.3)	43 (51.8)
Metabolism and nutrition disorders	13 (38.2)	17 (63.0)	11 (36.7)	30 (36.1)
Psychiatric disorders	9 (26.5)	7 (25.9)	15 (50.0)	22 (26.5)
Musculoskeletal and connective tissue disorders	5 (14.7)	5 (18.5)	16 (53.3)	8 (9.6)
Gastrointestinal disorders	3 (8.8)	6 (22.2)	12 (40.0)	10 (12.0)
Immune system disorders	3 (8.8)	1 (3.7)	13 (43.3)	1 (1.2)
Surgical and medical procedures	0	1 (3.7)	20 (66.7)	14 (16.9)
Ongoing comorbid conditions at trial entry				
Any ongoing condition, n (%)	32 (94.1)	27 (100.0)	29 (96.7)	68 (81.9)
Number of comorbid conditions per patient				
Mean (SD)	4.4 (4.6)	5.3 (4.3)	9.0 (6.7)	1.8 (1.6)
Median (Q1, Q3)	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	8.0 (3.0, 11.0)	1.0 (1.0, 2.0)
0, n (%)	2 (5.9)	0	1 (3.3)	15 (18.1)
1-2, n (%)	12 (35.3)	8 (29.6)	4 (13.3)	49 (59.0)
3-4, n (%)	9 (26.5)	7 (25.9)	4 (13.3)	10 (12.0)
5+, n (%)	11 (32.4)	12 (44.4)	21 (70.0)	9 (10.8)

Abbreviations: AED, antiepileptic drug; CBZ-CR, carbamazepine-controlled release; LCM, lacosamide; NA, not applicable; SD, standard deviation; SS, safety set.

^aFor SP0993, classification of seizures in the 1 y before screening is reported.

^bAEDs that were taken and stopped before initiation of lacosamide (SP0902: AEDs stopped 28 d before Visit 1; SP0973: AEDs stopped before start date of lacosamide).

during the 10-week monotherapy period (Figure 1B). Among patients who completed the monotherapy period ($n = 22$), 16 (72.7%) were 50% responders, 12 (54.5%) were 75% responders, and six (27.3%) were seizure-free.

3.3 | Lacosamide as adjunctive therapy to one baseline AED

In the observational trial, 571 patients took at least one dose of lacosamide, of whom 83 (14.5%) had CVEE (SS) (Table 2). Eighty-two patients with CVEE attended the final visit, of whom 69 (84.1%) were documented as continuing on lacosamide. The most common reasons for discontinuation ($\geq 5\%$ of patients) were AEs and withdrawn consent. The FAS included 75 patients and the mFAS included 71 patients.

In the SS, patients had a mean age of 62.6 years and 42 (50.6%) were female (Table 3). Patients had a median of one comorbid condition at baseline. Four (4.8%) patients had an ongoing cardiac disorder (atrial fibrillation [two], atrial tachycardia [one], myocardial infarction [one]). All patients were receiving treatment with one baseline AED at lacosamide initiation, most commonly ($\geq 5\%$ of patients) levetiracetam (39 [47.0%]), lamotrigine (11 [13.3%]), carbamazepine (10 [12.0%]), oxcarbazepine (seven [8.4%]), and valproic acid (seven [8.4%]). Median (range) duration of exposure to lacosamide was 183 (1, 280) days. Among patients who continued on lacosamide ($n = 69$), the median (range) maintenance dose was 300 (50, 600) mg/day.

Overall, 36 (43.4%) patients had a TEAE and 21 (25.3%) had TEAEs that were considered to be drug-related (Table 4). The most common TEAEs ($\geq 5\%$ of patients) were fatigue and dizziness. No cardiac TEAEs were reported. Two (2.4%) patients reported fall. Most TEAEs were mild or moderate in intensity; 10 (12.0%) patients reported severe TEAEs. Severe TEAEs in >1 patient were nausea (two [2.4%]), convulsion (two [2.4%]), and grand mal convulsion (two [2.4%]) (Table S1). Serious TEAEs were reported by nine (10.8%) patients, most commonly (≥ 2 patients) convulsion (two [2.4%]) and grand mal convulsion (two [2.4%]) (Table S1). Eight (9.6%) patients discontinued due to TEAEs (Table 4). TEAEs leading to discontinuation in ≥ 2 patients were nausea (three [3.6%]) and balance disorder (two [2.4%]).

During the last 3 months of the 6-month observation period, 60 (80.0%) patients in the FAS were 50% responders, 56 (74.7%) were 75% responders, and 42 (56.0%) were seizure-free (Figure 1C). In the mFAS, 58 (81.7%) patients were 50% responders, 54 (76.1%) were 75% responders, and 40 (56.3%) were seizure-free.

4 | DISCUSSION

These exploratory *post hoc* analyses suggested that lacosamide was generally well tolerated and effective in improving seizure control in patients with CVEE, when used as initial monotherapy in newly diagnosed patients; in patients converting from their existing AED

regimen to lacosamide monotherapy; and when added to one concomitant AED in routine clinical practice.

In the small subgroup of patients with CVEE in the initial monotherapy trial, a higher proportion of patients on lacosamide than carbamazepine-CR remained on the first target dose level. No patients on lacosamide escalated to the highest permitted dose. Lacosamide showed favorable tolerability in comparison with carbamazepine-CR with lower incidences of drug-related TEAEs and discontinuations due to TEAEs, despite the higher mean age of patients in the lacosamide group. In line with these results, a subgroup analysis of patients aged ≥ 65 years enrolled in the monotherapy trial ($n = 119$) suggested a better tolerability profile with lacosamide than carbamazepine-CR; however, the incidence of fall was higher with lacosamide (9.7% [$n = 62$]; 1.8% [$n = 57$]).¹⁴ In the CVEE subgroup, two (7.4%) patients on lacosamide and one (2.9%) on carbamazepine-CR reported a TEAE of fall. It should be noted that there was some overlap between patients in the CVEE and elderly subgroups (42.6% of patients with CVEE were ≥ 65 years of age). In patients with CVEE treated with lacosamide, the incidence of discontinuations due to TEAEs (11.1% [$n = 34$]) was numerically lower than in the elderly subgroup (21.0% [$n = 62$]) and similar to that observed in the overall trial population (10.6% [$n = 444$]).¹⁴ All efficacy outcomes assessed in patients with CVEE (patients remaining seizure-free for 6 and 12 months at last evaluated dose, and from the date of first dose; Kaplan-Meier estimated 6- and 12-month seizure freedom) showed numerically higher seizure freedom on lacosamide compared to carbamazepine-CR. Kaplan-Meier estimated 6-month seizure freedom at last evaluated dose was 95.5% ($n = 27$) on lacosamide and 82.0% ($n = 34$) on carbamazepine-CR in patients with CVEE, and similar with lacosamide and carbamazepine-CR in the overall population (89.8% [$n = 444$]; 91.1% [$n = 442$]) and the elderly subgroup (93.6% [$n = 62$]; 92.3% [$n = 57$]).¹⁴

Patients with CVEE in the conversion to monotherapy trial were relatively young (mean age 42 years), had a long history of epilepsy (median 10 years since diagnosis), a high baseline seizure frequency despite ongoing treatment with one or two AEDs, and a high number of comorbid conditions (median 8.0). Furthermore, 60% of patients had failed two or more AEDs prior to initiation of lacosamide, suggesting a drug-resistant population. The incidences of TEAEs and TEAEs leading to discontinuation (86.7%; 16.7% [$n = 30$]) in the CVEE subgroup were generally similar to those reported for the overall trial population (84.5%; 16.2% [$n = 425$]),¹⁵ although comparisons are limited by the substantial difference in sample size. Similar to the overall population, the incidences of the most common TEAEs (excluding convulsion) were higher during titration than lacosamide monotherapy. The high starting dose of lacosamide (200 mg/day) and fixed titration schedule may have contributed to the higher incidence of TEAEs during titration. The preferred term convulsion was used to record all changes of seizure type and severity, including emergence of less severe seizure types despite resolution of more severe seizures.¹⁵ Despite their long epilepsy duration, high baseline seizure frequency, and high number of previously tried AEDs, 56.7% of patients with CVEE ($n = 30$) were

TABLE 4 Treatment-emergent adverse events (TEAEs) in patients with cerebrovascular epilepsy etiology (SS)

	Initial monotherapy with LCM or CBZ-CR		Conversion to LCM monotherapy	LCM adjunctive to one baseline AED
	CBZ-CR (n = 34)	LCM (n = 27)	LCM (n = 30)	LCM (n = 83)
Any TEAE, n (%)	27 (79.4)	20 (74.1)	26 (86.7)	36 (43.4)
Drug-related TEAEs, n (%)	17 (50.0)	8 (29.6)	20 (66.7)	21 (25.3)
Serious TEAEs, n (%)	7 (20.6)	5 (18.5)	3 (10.0)	9 (10.8)
Severe TEAEs, n (%)	4 (11.8)	4 (14.8)	8 (26.7)	10 (12.0)
Discontinuation due to TEAEs, n (%)	7 (20.6)	3 (11.1)	5 (16.7)	8 (9.6)
Deaths, n (%)	0	1 (3.7)	0	0
TEAEs reported by ≥10% patients in any group in any of the three trials, n (%) (<i>numbers meeting this criterion are bolded</i>)				
Headache	5 (14.7)	3 (11.1)	4 (13.3)	1 (1.2)
Dizziness	4 (11.8)	3 (11.1)	8 (26.7)	6 (7.2)
Fatigue	0	3 (11.1)	4 (13.3)	12 (14.5)
Somnolence	3 (8.8)	0	4 (13.3)	2 (2.4)
Cognitive disorder	1 (2.9)	1 (3.7)	4 (13.3)	1 (1.2)
Tremor	1 (2.9)	1 (3.7)	3 (10.0)	4 (4.8)
Convulsion ^a	1 (2.9)	0	5 (16.7)	2 (2.4)
Dry mouth	0	0	3 (10.0)	0
Upper respiratory tract infection	0	1 (3.7)	3 (10.0)	0

Abbreviations: AED, antiepileptic drug; CBZ-CR, carbamazepine-controlled release; LCM, lacosamide; MedDRA, Medical Dictionary for Regulatory Activities; SS, safety set.

^aPreferred term "convulsion" captures both worsening of seizure conditions and improvements (emergence of less severe seizure types); therefore, the incidence of convulsion may be an overestimate of the number of patients with worsening seizures.

50% responders and 20.0% became seizure-free during lacosamide monotherapy (overall population [n = 425]; 50% responders: 42.4%; seizure-free: 9.2%).¹⁵ These exploratory data suggest that conversion to lacosamide monotherapy may be beneficial for select patients with CVEE whose seizures are not controlled on their existing AED regimens.

In comparison with the conversion to monotherapy trial, the observational study included patients with CVEE who had an older age of epilepsy onset, shorter epilepsy duration (median 3 years since diagnosis), lower baseline seizure frequency and likely represent a less drug-resistant population (38.6% had failed two or more lifetime AEDs). Incidences of TEAEs and TEAEs leading to discontinuation in patients with CVEE (43.4%; 9.6% [n = 83]) were similar to those reported for the overall study population (48.5%; 10.6% [n = 571]) and for a subgroup of patients ≥65 years of age (45.5%; 8.2% [n = 110]).¹⁶ 50% responder and seizure freedom rates in the CVEE subgroup (80.0%; 56.0% [n = 75]) were numerically higher than in the overall population (71.8%; 44.3% [n = 515]).¹⁶ Analyses of patients treated with in-label doses of adjunctive lacosamide (up to 400 mg/day) showed similar effectiveness in the CVEE subgroup (50% responders: 81.7%; seizure freedom: 56.3% [n = 71]) and the elderly subgroup (81.1%; 56.7% [n = 90]). There was an overlap between the CVEE and elderly subgroups (56.6% of patients with CVEE were aged ≥65 years).

The initial monotherapy¹⁴ and conversion to monotherapy¹⁵ trials excluded patients who had sick sinus syndrome without a pacemaker, second- or third-degree atrioventricular block, or any other clinically significant electrocardiogram abnormalities, myocardial infarction in the previous 3 months, or New York Heart Association Class III or IV heart failure. Eligibility criteria for the observational study were defined by the lacosamide 2008 SmPC. Per the SmPC, lacosamide is contraindicated in patients with second- or third-degree atrioventricular block; therefore, these patients were not to be enrolled.¹⁶ Ongoing cardiac disorders were reported in six patients with CVEE taking lacosamide in the initial monotherapy trial, one patient in the conversion to monotherapy trial, and four in the observational study. A total of three cardiac TEAEs were reported during lacosamide treatment in patients with CVEE. Analyses of pooled cardiac safety data from three randomized, placebo-controlled trials of adjunctive lacosamide in patients with focal seizures showed no clear cardiac effects at the maximum recommended dose (400 mg/day) other than a small dose-related increase in PR interval.¹⁷ Lacosamide should be used with caution in patients with underlying proarrhythmic conditions (known cardiac conduction problems, severe cardiac disease, and cardiac sodium channelopathies), as well as in patients taking concomitant medications that affect cardiac conduction or prolong the PR interval.⁸

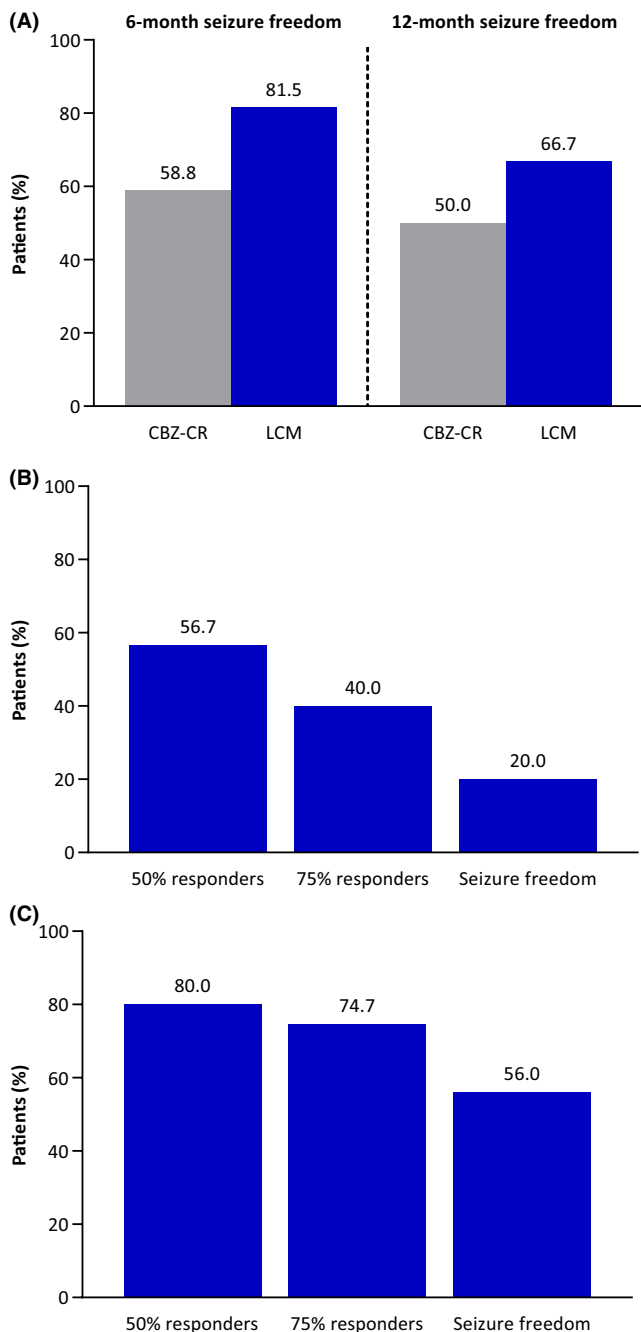


FIGURE 1 Efficacy/effectiveness outcomes in patients with cerebrovascular epilepsy etiology. A, Initial monotherapy with lacosamide or carbamazepine-CR: proportion of patients who completed 6 and 12 mo of treatment and were seizure-free at the last evaluated dose (FAS; CBZ-CR, $n = 34$; LCM, $n = 27$). B, Conversion to lacosamide monotherapy: 50% and 75% responder rates and seizure freedom during the 10-wk lacosamide monotherapy period (SS; $n = 30$). C, Lacosamide as adjunctive therapy to one baseline AED: 50% and 75% responder rates and seizure freedom during the last 3 months of the 6-month observation period (FAS; $n = 75$). AED, antiepileptic drug; CBZ-CR, carbamazepine-controlled release; FAS, full analysis set; LCM, lacosamide; SS, safety set

Considerations for AED treatment of patients with post-stroke epilepsy include potential effects on vascular risk profile.³ Treatment with enzyme-inducing AEDs such as carbamazepine is known to increase serum lipid levels, an arteriosclerotic risk factor.^{18,19} A *post hoc* analysis of data from the initial monotherapy trial showed no effects of lacosamide on the lipid profile of adults with newly diagnosed epilepsy, whereas lipid levels increased during carbamazepine-CR treatment.²⁰ Furthermore, a small open-label trial has shown favorable changes in lipid profiles in young males with focal seizures, following a switch from carbamazepine to lacosamide as adjunctive treatment to levetiracetam.²¹

As these were exploratory *post hoc* analyses based on small numbers of patients, the data should be interpreted with caution. Information on the specific cause of cerebrovascular epilepsy was not systematically collected at baseline of the three trials. The three trials differed in their designs, durations, and patient eligibility criteria. As such, the CVEE population in each trial differed in terms of age at diagnosis, epilepsy duration, number of AEDs failed prior to lacosamide initiation, and baseline seizure frequency.

Despite their limitations, these exploratory *post hoc* analyses suggested that lacosamide was relatively well tolerated and effective in select patients with CVEE, with data from the monotherapy trial suggesting numerically better efficacy than carbamazepine-CR. These results, together with lacosamide's favorable pharmacokinetic profile,²² low potential for clinically relevant drug-drug interactions,²³ and no effect on lipid levels,²⁰ suggest lacosamide may be a suitable option as monotherapy or adjunctive therapy for select patients with CVEE.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Underlying data from SP0902 and SP0993 in this manuscript may be requested by qualified researchers 6 months after product or indication approval in the US and/or EU, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient data and redacted study documents which may include the following: raw datasets, analysis-ready datasets, study protocol, blank case report form, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Before use of the data, proposals need to be approved by an independent review panel at www.clinicalstudydatarequest.com and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal. UCB Pharma does not share data from non-interventional trials (SP0973) that are included in this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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