


# Effectiveness and tolerability of lacosamide as add-on therapy in patients with brain tumor–related epilepsy: Results from a prospective, noninterventional study in European clinical practice (VIBES)

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## Abstract

**Objective:** To evaluate the effectiveness and tolerability of lacosamide added to one or two antiepileptic drugs (AEDs) in the treatment of patients with brain tumor–related epilepsy (BTRE), and to evaluate patients' global impression of change and quality of life (QoL).

**Methods:** This was a prospective, multicenter, single-arm, noninterventional study with a 6-month observation period (EP0045; NCT02276053). Eligible patients ( $\geq 16$  years old) had active BTRE secondary to low-grade glioma (World Health Organization grade 1 and 2) and were receiving treatment with one or two AEDs at baseline. Lacosamide was initiated by the treating physician in the course of routine clinical practice. Primary outcomes were 50% responders ( $\geq 50\%$  reduction in focal seizure frequency from baseline) and Patient's Global Impression of Change (PGIC) at month 6. Secondary outcomes included seizure-free status and Clinical Global Impression of Change (CGIC) at month 6, change in QoL (5-Level EuroQol-5 Dimension Quality of Life Assessment) and symptom outcomes (MD Anderson Symptom Inventory–Brain Tumor) from baseline to month 6, and Kaplan-Meier estimated 6-month retention on lacosamide. Safety variables included adverse drug reactions (ADRs).

**Results:** Patients were recruited from 24 sites in Europe. Ninety-three patients received lacosamide (mean [standard deviation] age = 44.5 [14.7] years; 50 [53.8%] male; median baseline focal seizure frequency = five seizures/28 days [range = 1–280]), of whom 79 (84.9%) completed the study. At 6 months, 66 of 86 (76.7%) patients were 50% responders and 30 of 86 (34.9%) were seizure-free. Improvements on PGIC were reported by 49 of 76 (64.5%) patients. Based on CGIC, 52 of 81 (64.2%) patients improved. QoL and symptoms outcome measures remained stable.

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#### Funding information

UCB Pharma

Kaplan-Meier estimated 6-month retention rate was 86.0% (N = 93). Fifteen (16.1%) patients reported ADRs; four (4.3%) had ADRs leading to discontinuation (N = 93). **Significance:** Results of this prospective, noninterventional study suggest that add-on lacosamide is effective and generally well tolerated in patients with BTRE.

#### KEYWORDS

antiepileptic drug, low-grade glioma, quality of life, retention, seizures

## 1 | INTRODUCTION

Seizures are present in 15% to 95% of patients with brain tumors, with prevalence varying according to tumor type and grade.<sup>1,2</sup> A meta-analysis of four randomized controlled trials and eight cohort studies, which included >1000 patients, indicated that seizure incidence was higher in patients with primary compared with metastatic brain tumors.<sup>3</sup> Diffuse low-grade gliomas are one of the most highly epileptogenic tumor types, with up to 83% of patients experiencing epileptic seizures as a presenting symptom.<sup>4</sup> Approximately 50% of patients with low-grade glioma may have drug-resistant epilepsy prior to tumor surgery.<sup>5</sup>

When uncontrolled, brain tumor-related epilepsy (BTRE) has a negative impact on patient quality of life and may result in significant morbidity and cognitive deterioration.<sup>6</sup> Epilepsy is often considered the most important risk factor for long-term disability in patients with brain tumors<sup>2</sup>; however, there are limited data available for the treatment of seizures with antiepileptic drugs (AEDs) in this population. Difficulties in the management of BTRE include treatment-resistant epilepsy, the risk of cognitive side effects, and potential interactions between AEDs and chemotherapeutic agents.<sup>7</sup> The use of enzyme-inducing AEDs may accelerate the metabolism of concomitant corticosteroids and chemotherapeutic agents.<sup>6,8-10</sup> Guidelines for the management of patients with BTRE therefore advise against the use of enzyme-inducing AEDs and recommend newer generation AEDs as first-choice treatment, to be started after the first seizure.<sup>11</sup>

Lacosamide is a non-enzyme-inducing AED indicated for the treatment of focal (partial onset) seizures in patients  $\geq 4$  years of age in the European Union and the USA.<sup>12,13</sup> Published data from retrospective and prospective studies has shown good tolerability and effectiveness of lacosamide in patients with BTRE.<sup>14-18</sup> The primary objective of the current study was to evaluate the effectiveness of lacosamide added to one or two AEDs in the treatment of patients with BTRE, based on the 50% responder rate and patients' global impression of change. Tolerability and quality of life (QoL) were also assessed.

#### Key Points

- A total of 93 patients with BTRE were enrolled and treated with lacosamide; 79 (84.9%) completed the study
- At month 6, 76.7% of patients had at least a 50% reduction in focal seizure frequency from baseline and 34.9% were seizure-free
- Overall, 64.5% of patients and 64.2% of clinicians reported improvement with the addition of lacosamide using Global Impression of Change scales
- Quality of life (EQ-5D-5L) and symptom outcomes (MDASI-BT) remained stable from baseline to month 6
- Lacosamide was generally well tolerated in patients with BTRE; observed ADRs were consistent with the known safety profile of lacosamide

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

VIBES (EP0045; clinicaltrials.gov: NCT02276053) was a prospective, multicenter, single-arm, noninterventional study conducted at specialized centers in six European countries between November 2014 and December 2017. At each site, the study was approved by the appropriate national scientific and ethical committees in accordance with local requirements and laws. The decision to initiate lacosamide treatment was made by the treating physician in the course of routine clinical practice. Patients attending clinic with active epilepsy (not controlled by existing AEDs and requiring an additional AED) were informed about the VIBES study when the physician considered lacosamide to be the best AED choice. Participation in the study was based on shared decision-making between the physician and patient. If, on discussion, an alternative AED was considered a better choice, patients were not enrolled. Patients ( $\geq 16$  years of age) were eligible for inclusion if

they had a diagnosis of BTRE secondary to low-grade glioma (World Health Organization [WHO] grade 1 to 2 at enrollment), were naive to lacosamide (or treatment with lacosamide started no earlier than 7 days before enrollment), and were receiving treatment with one or two AEDs at baseline. Additional eligibility criteria were at least one focal seizure in the 8 weeks before the start of lacosamide treatment, a Karnofsky performance status score of  $\geq 60$ , and a maximum of four different prior AEDs (AEDs that were received and stopped before the first dose of study drug). Before study enrollment, each patient (or legal representative) was required to provide written informed consent for the use of their medical data.

Dosages of lacosamide and other medications were determined at the discretion of the physician. All visits and assessments were conducted per routine clinical practice, with an observation period of up to 6 months after initiation of lacosamide treatment. Visits were planned to occur every 3 months (visit 1: baseline; visit 2: after ~3 months; visit 3: after ~6 months). Patients were withdrawn from the study if they discontinued lacosamide, required an increase in dose of the AEDs the patient was receiving at baseline, or required treatment with more than two AEDs (other than lacosamide). For patients who discontinued early, visit 3 assessments were performed at the withdrawal visit.

## 2.2 | Outcome measures

The two primary outcome measures were the 50% responder rate (percentage of patients with  $\geq 50\%$  reduction in focal seizure frequency/28 days from baseline to month 6) and the Patient Global Impression of Change (PGIC; a 7-point categorical rating scale in which the patient rates the changes in functioning over time from 1 = very much improved to 7 = very much worse) at month 6.

Secondary outcomes included seizure-free status, actual and percentage change from baseline in focal seizure frequency/28 days, and Clinical Global Impression of Change (CGIC; clinician rates changes from 1 to 7) at month 6. QoL was assessed using the patient-rated 5-Level EuroQol-5 Dimension Quality of Life Assessment (EQ-5D-5L) utility score (assessment of mobility, self-care, usual activities, pain/discomfort, anxiety/depression; higher scores indicate a lower QoL) and visual analogue scale (health state rated from 0 = worst imaginable to 100 = best imaginable).<sup>19</sup> The patient-rated MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT) questionnaire was used to assess symptom severity.<sup>20</sup> This scale includes four measures: *core symptom severity* (based on 13 core symptoms), *module symptom severity* (based on nine brain tumor-specific symptoms: weakness on one side of the body, difficulty understanding, difficulty speaking, seizures, difficulty

concentrating, vision, change in appearance, change in bowel pattern, and irritability), *total severity* (core symptom severity and module symptom severity combined), and *interference with daily living*. Higher scores indicate greater symptom severity/interference.

Additional secondary outcomes included 6-month retention on lacosamide, time to discontinuation of lacosamide treatment from the date of first dose, and discontinuation of lacosamide because of lack of effectiveness (lack of efficacy or adverse drug reaction [ADR; an adverse event considered to be related to the study drug by the investigator]). Safety outcomes included ADRs and withdrawal due to ADRs.

## 2.3 | Statistical analyses

Analyses were carried out in the safety set (SS; all patients who received at least one dose of lacosamide) and full analysis set (FAS; all SS patients who had at least one postbaseline PGIC rating or seizure assessment).

All statistical analyses were performed in an exploratory manner; all variables were summarized using descriptive statistics, and no inferential analyses were conducted. One hundred patients were planned for enrollment, to obtain 93 evaluable patients. This sample size was chosen based on an expected 6-month responder rate of 60%, with an expected precision in the 95% confidence interval (CI) of approximately  $\pm 10\%$ . Analyses of effectiveness were primarily performed for the FAS, with percentages based on patients with available data. Baseline seizure frequency was based on a 56-day historical seizure count. For visits 2 and 3, the number of seizures since the previous visit was used to calculate the seizure frequency at the visit. For the month 6 assessment, data collected  $>135$  days after baseline (visit 3) were used unless missing, in which case, data collected  $\leq 135$  days after baseline (visit 2) were used. The 6-month retention rate and median time to discontinuation were derived using Kaplan-Meier estimates. Patients who completed the study were censored on the date of final lacosamide administration, or date of study termination if date of final lacosamide administration was unavailable.

As a post hoc sensitivity analysis, assessments of 50% responder rates, seizure freedom, PGIC scores, and CGIC scores were also performed for the SS. For the SS analyses, patients with missing data were considered to be nonresponders/not seizure-free, and were included as a separate "missing" category in the PGIC and CGIC assessments.

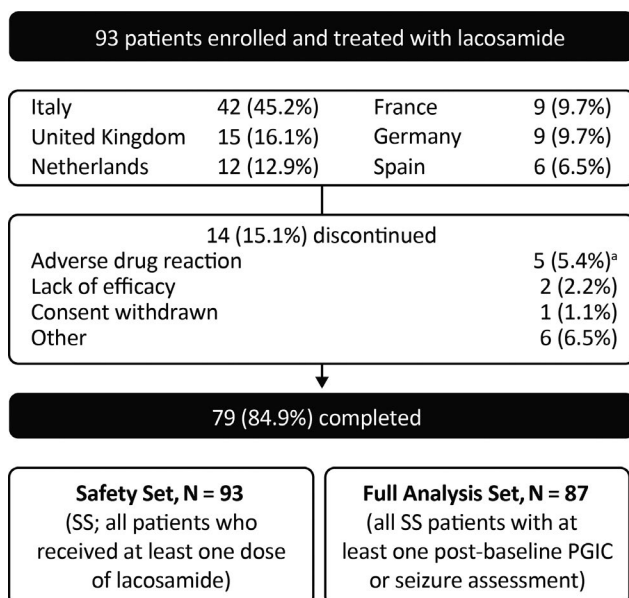
Post hoc subgroup analyses of 50% responder rate, seizure freedom, and PGIC were performed for patients with confirmed low-grade glioma (WHO grade 1 or 2), and for patients with and without tumor treatment (defined as surgery or radiotherapy related to tumor within 90 days before/after first lacosamide dose, or chemotherapy during lacosamide treatment).

### 3 | RESULTS

#### 3.1 | Patients

A total of 93 patients were enrolled from 24 sites in Italy, the United Kingdom, the Netherlands, Germany, France, and Spain (Figure 1). All 93 patients received at least one dose of lacosamide and were included in the SS; 79 (84.9%) patients completed the study, and 14 (15.1%) discontinued (Figure 1). Eighty-seven patients were included in the FAS. All patients except one received lacosamide doses of  $\leq 400$  mg/d, which reflects the on-label use of lacosamide.

In the SS, patients had a mean (standard deviation [SD]) age of 44.5 (14.7) years; with the exception of one patient (16 years of age), all were  $>18$  years of age. Patients had a median of 2 years since first tumor diagnosis, and 75.3% had a Karnofsky performance status score of  $>80$  (Table 1). Eighty-four (90.3%) patients had low-grade glioma, one (1.1%) patient had grade 3 glioma, three (3.2%) had suspected glioma, three (3.2%) had meningioma, one (1.1%) had craniopharyngioma, and one (1.1%) had a histologically unverified tumor. During lacosamide treatment, 19 (20.4%) patients received antineoplastic agents, 15 (16.1%) received radiotherapy, and eight (8.6%) had tumor surgery. At baseline, the median focal seizure frequency was five seizures/28 days (range = 1-280) in both the SS and FAS ( $n = 92$  and  $n = 86$  evaluable patients, respectively). All patients were receiving AED treatment at baseline; levetiracetam monotherapy was the most common AED regimen, received by 45 (48.4%) patients (Table 1).



**FIGURE 1** Patient disposition and discontinuation reasons.

<sup>a</sup>In one patient, drug was withdrawn due to adverse event, but the relationship to study medication was not recorded. PGIC, Patient Global Impression of Change

During the study, patients in the SS had a mean (SD) lacosamide treatment duration of 171.6 (58.1) days (FAS: 182.7 [41.1]) with a mean (SD) modal daily dose of 220.7 (94.9) mg/day (FAS: 229.0 [91.5]). In the FAS, 75 (86.2%) patients initiated lacosamide at a titration dose ( $<200$  mg/d) and 12 (13.8%) at a high starting dose ( $\geq 200$  mg/d).

#### 3.2 | Effectiveness

In the FAS, 86 patients had evaluable data for seizure response assessments. Of these patients, 66 (76.7%) were 50% responders and 30 (34.9%) were seizure-free at 6 months. Median (Q1, Q3) change in focal seizure frequency/28 days was  $-2.9$  ( $-9.1$ ,  $-0.9$ ), and median (Q1, Q3) percentage change was  $-85.2$  ( $-100$ ,  $-55.5$ ). In the SS (sensitivity analysis,  $N = 93$ ), seven (7.5%) patients had missing data, 66 (71.0%) were 50% responders, and 30 (32.3%) were seizure-free.

In the FAS, 76 patients had evaluable PGIC data. Of these patients, 49 (64.5%) had an improvement, 17 (22.4%) had no change, and 10 (13.2%) had a worsening at 6 months (Figure 2). For the CGIC, 81 patients had evaluable data, of whom 52 (64.2%) had an improvement, 19 (23.5%) had no change, and 10 (12.3%) had a worsening (Figure 2). In the SS (sensitivity analysis,  $N = 93$ ), based on PGIC assessments, 49 (52.7%) patients improved, 17 (18.3%) had no change, and 10 (10.8%) worsened (data were missing for 17 [18.3%] patients). Based on the CGIC assessments, 52 (55.9%) patients improved, 19 (20.4%) had no change, and 10 (10.8%) worsened (data were missing for 12 [12.9%] patients).

Post hoc subgroup analyses were performed for patients with confirmed low-grade glioma (WHO grade 1 or 2) and patients with and without tumor treatment. In the FAS, 80 patients with confirmed low-grade glioma had evaluable data for seizure assessments. At 6 months, 60 (75.0%) were 50% responders, and 27 (33.8%) were seizure-free. PGIC data were available for 72 patients, of whom 47 (65.3%) had an improvement, 15 (20.8%) had no change, and 10 (13.9%) worsened (Figure 3). Evaluable seizure data were available for 33 patients with tumor treatment and 53 without (FAS). At 6 months, 27 (81.8%) patients with tumor treatment and 39 (73.6%) patients without tumor treatment were 50% responders. Twelve (36.4%) patients with tumor treatment and 18 (34.0%) patients without tumor treatment were seizure-free. Evaluable PGIC data were available for 30 patients with tumor treatment, of whom 19 (63.3%) improved, six (20.0%) had no change, and five (16.7%) worsened (Figure 3). In the subgroup of patients without tumor treatment, 46 had evaluable PGIC data, of whom 30 (65.2%) improved, 11 (23.9%) had no change, and five (10.9%) worsened.

In the overall population (FAS), mean (SD) changes in the EQ-5D-5L visual analogue scale ( $n = 72$ ) and utility score

( $n = 73$ ) from baseline to month 6 were 1.3 (16.4) and  $-0.01$  (0.20), respectively. For the MDASI-BT, mean (SD) change from baseline to month 6 was 0.1 (1.3) for core symptom severity ( $n = 73$ ),  $-0.1$  (1.6) for mean module symptom severity (brain tumor-specific items;  $n = 70$ ), 0.0 (1.2) for mean total severity ( $n = 73$ ), and  $-0.5$  (2.4) for mean interference ( $n = 70$ ).

At month 6, 59 (63.4%) patients in the SS and 59 (67.8%) patients in the FAS were still receiving lacosamide. Kaplan-Meier estimated 6-month retention was 86.0% (95% CI = 79.0-93.1) for the SS and 92.0% (95% CI = 86.2-97.7) for the FAS. Kaplan-Meier estimates for the time to discontinuation of lacosamide from the date of first dose are shown in Figure 4. Overall, seven (7.5%) patients in the SS discontinued lacosamide due to lack of effectiveness. Of these, five (5.4%) patients discontinued due to an ADR and two (2.2%) due to lack of efficacy. In the FAS, five (5.7%) patients discontinued lacosamide due to lack of effectiveness, three (3.4%) due to an ADR and two (2.3%) due to lack of efficacy.

### 3.3 | Safety and tolerability

Overall, ADRs were reported by 15 (16.1%) patients in the SS (Table 2). The most common ADRs ( $\geq 2\%$  of patients) were vertigo, headache, nausea, and asthenia. One patient had partial seizures resulting in hospitalization, which was considered to be a serious ADR in the opinion of the investigator. The ADR was resolved in 1 day, and the dose of lacosamide was increased. Four (4.3%) patients had ADRs that led to discontinuation; two patients discontinued due to vertigo, one discontinued due to rash, and one discontinued due to nausea, lack of efficacy (recorded as an ADR per regulatory reporting requirements), gait disturbance, dizziness, headache, and memory impairment. Two patients died during the study, one due to brain neoplasm and status epilepticus, and one due to brain edema. Neither death was considered to be related to study medication.

## 4 | DISCUSSION

The results of this open-label, noninterventional study suggest that add-on lacosamide is effective and generally well tolerated in patients with BTRE. Enrolled patients had a relatively high seizure frequency at baseline despite ongoing AED treatment, most commonly with levetiracetam monotherapy. Seizure assessments showed that the majority of patients responded to add-on lacosamide, with 76.7% (FAS) reporting a 50% reduction in focal seizure frequency and 34.9% attaining seizure freedom at 6 months. Per the study protocol, a diagnosis of BTRE secondary to low-grade glioma was required

for inclusion; however, a degree of heterogeneity in tumor types was observed. Post hoc analyses were therefore conducted in a subgroup of patients with confirmed low-grade glioma. Results of these analyses indicate the effectiveness of lacosamide in this patient population.

Results are consistent with the responder rates observed in three prospective studies that investigated the effectiveness of add-on lacosamide in heterogeneous groups of patients with high- or low-grade gliomas and uncontrolled focal seizures.<sup>14-15,18</sup> One of these was an observational study ( $N = 71$ ) which found a 50% responder rate of 76% with add-on lacosamide at 6 months; 43% of patients were seizure-free at 6 months.<sup>15</sup> In that study, levetiracetam was also the most frequent concomitant AED. Another study compared the effectiveness of add-on lacosamide ( $n = 22$  evaluable patients) with a historical control group treated with add-on levetiracetam ( $n = 19$ ).<sup>18</sup> The 6-month 50% responder rate in that study was higher with lacosamide than with levetiracetam (86.4% vs 73.7%), although the difference was not statistically significant, potentially due to the low number of patients. At 6 months, 31.8% of patients on lacosamide were seizure-free. The last study (single center,  $N = 14$ , approximately 6 months follow-up) reported a 50% responder rate of 78.6% at final follow-up; 42.9% of patients were seizure-free.<sup>14</sup>

The effectiveness of lacosamide in controlling seizures has also been investigated in studies that included patients with a range of brain tumor types, including gliomas as well as meningioma, medulloblastoma, and brain metastasis.<sup>16-17,21</sup> Most of these studies were retrospective, patients had approximately 6 months of follow-up, and the majority received lacosamide as add-on therapy. Fifty percent responder rates of 66.3%-84.6% and seizure freedom of 30.8%-53.8% were reported at 6 months.<sup>16-17,21</sup> Slight differences in effectiveness may be partly due to variations in trial design (prospective vs retrospective), tumor types, and tumor grade between the patient populations, as seizures secondary to low-grade tumors may be more treatment-resistant.<sup>22</sup>

In the current study, 33 of 86 patients with evaluable seizure data (FAS) received antitumor treatments, including surgery or radiotherapy within 90 days before or after starting lacosamide, or chemotherapy during lacosamide treatment, which may have contributed to a reduction in seizures in some patients.<sup>23-26</sup> Post hoc analyses were therefore carried out in subgroups of patients with and without tumor treatment. In both subgroups, the majority of patients were responders, although the 50% responder rate was numerically higher ( $\sim 8\%$ ) among patients with tumor treatment. These results indicate that the observed reductions in seizure frequency were likely due to lacosamide, although per the study design, there was no placebo group for comparison. Seizure frequency may have also been influenced by the natural evolution of the tumor. These post hoc analyses should be interpreted with

TABLE 1 Patient demographics and baseline characteristics

	Safety set, N = 93	Full analysis set, N = 87
Demographics		
Age, y		
Mean (SD)	44.5 (14.7)	43.4 (14.2)
Median (range)	43.0 (16-83)	42.0 (16-78)
≥16 to <18 y, n (%)	1 (1.1)	1 (1.1)
>18 to <65 y, n (%)	82 (88.2)	78 (89.7)
≥65 y, n (%)	10 (10.8)	8 (9.2)
Male, n (%)	50 (53.8)	47 (54.0)
Tumor characteristics at baseline		
Time since tumor first diagnosed, y		
Mean (SD)	5.0 (7.2)	4.9 (7.1)
Median (range)	2.0 (0-32)	2.0 (0-32)
Type of tumor, n (%)		
Oligodendroglioma	32 (34.4)	30 (34.5)
Astrocytoma	29 (31.2)	29 (33.3)
Mixed (oligo-astro)	13 (14.0)	13 (14.9)
Other <sup>a</sup>	19 (20.4)	15 (17.2)
Tumor WHO grade		
1	11 (11.8)	10 (11.5)
2	80 (86.0)	76 (87.4)
3	1 (1.1)	1 (1.1)
Missing	1 (1.1)	0
Karnofsky performance status score, n (%)		
<60	0	0
60	4 (4.3)	2 (2.3)
70	5 (5.4)	5 (5.7)
80	14 (15.1)	11 (12.6)
90	48 (51.6)	47 (54.0)
100	22 (23.7)	22 (25.3)
Any antineoplastic agents received during lacosamide treatment, n (%)		
Temozolomide	16 (17.2)	16 (18.4)
Lomustine	3 (3.2)	3 (3.4)
Procarbazine	3 (3.2)	3 (3.4)
Vincristine	3 (3.2)	3 (3.4)
Bevacizumab	2 (2.2)	2 (2.3)
Any radiotherapy received during lacosamide treatment, n (%)		
Any tumor surgery during lacosamide treatment, n (%) <sup>b</sup>	8 (8.6)	8 (9.2)
Epilepsy characteristics at baseline		
Historical seizure type, n (%)		

(Continues)

TABLE 1 (Continued)

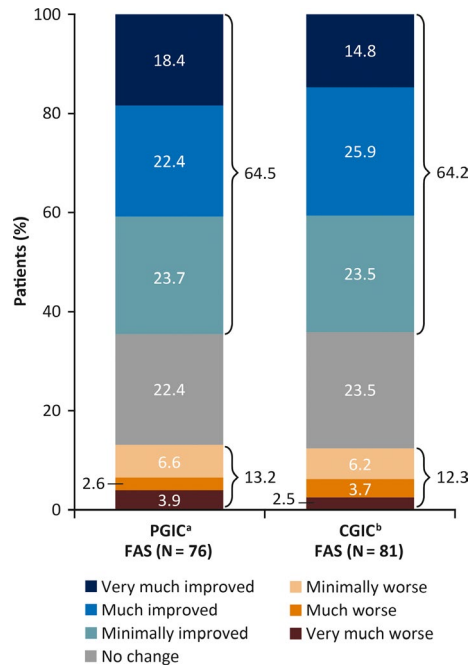
	Safety set, N = 93	Full analysis set, N = 87
Focal (partial onset) with secondary generalization	—	6 (6.9)
Focal (partial onset) without secondary generalization	—	57 (65.5)
Both	—	17 (19.5)
Missing	—	7 (8.0)
Number of prior AEDs, n (%) <sup>c</sup>		
0	55 (59.1)	52 (59.8)
1	25 (26.9)	25 (28.7)
2	11 (11.8)	8 (9.2)
3	2 (2.2)	2 (2.3)
AED therapy type patients were receiving at baseline, n (%)		
Monotherapy	62 (66.7)	59 (67.8)
Combination therapy with two AEDs	29 (31.2)	26 (29.9)
Combination therapy with three AEDs	2 (2.2)	2 (2.3)
Most common (≥2% in either dataset) AED monotherapies at baseline, n (%)		
Levetiracetam	45 (48.4)	42 (48.3)
Lamotrigine	6 (6.5)	6 (6.9)
Oxcarbazepine	3 (3.2)	3 (3.4)
Valproate sodium/valproic acid	3 (3.2)	3 (3.4)
Carbamazepine	2 (2.2)	2 (2.3)
Most common (≥2% in either dataset) AED add-on therapies at baseline, n (%)		
Lamotrigine + levetiracetam	6 (6.5)	5 (5.7)
Carbamazepine + phenobarbital	5 (5.4)	5 (5.7)
Clobazam + levetiracetam	3 (3.2)	1 (1.1)
Levetiracetam + oxcarbazepine	3 (3.2)	3 (3.4)
Lamotrigine + levetiracetam	3 (3.2)	3 (3.4)

Abbreviations: AED, antiepileptic drug; SD, standard deviation; WHO, World Health Organization.

<sup>a</sup>Other: unspecified glioma, gliomatosis cerebri, ganglioglioma, dysembryoplastic neuroepithelial tumor, glioneuronal tumor, pilocytic astrocytoma, suspected glioma, meningioma, craniopharyngioma, or histologically unverified tumor.<sup>b</sup>Reported terms: debulking surgery, elective debulking of brain tumor, gross total resection, partial resection or resection.<sup>c</sup>AEDs with an end date before the first dose of study drug.

caution given the small number of evaluable patients (n = 33) with tumor treatment.

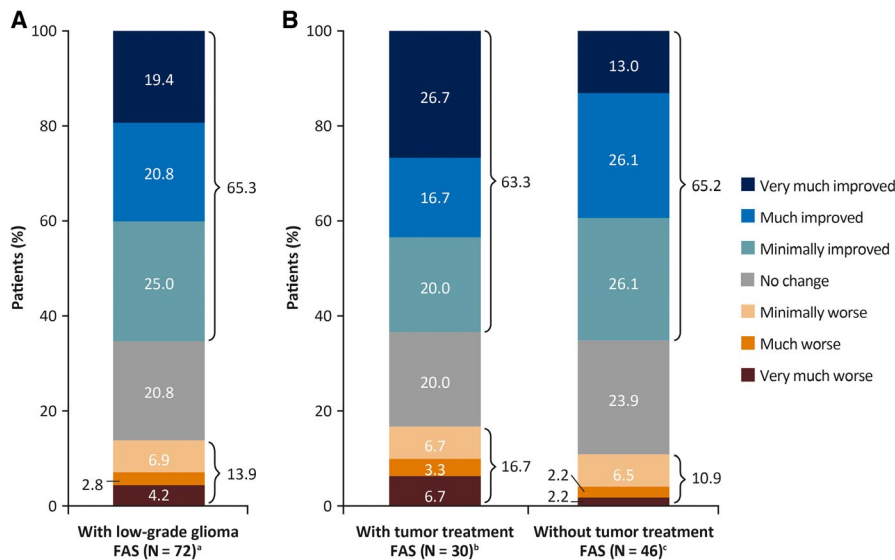
In the overall study population, effectiveness of lacosamide was supported by the high Kaplan-Meier estimated 6-month retention rate (86%, SS), with few patients discontinuing due to ADRs or lack of efficacy. Kaplan-Meier estimated 6-month retention was similar to that reported for a



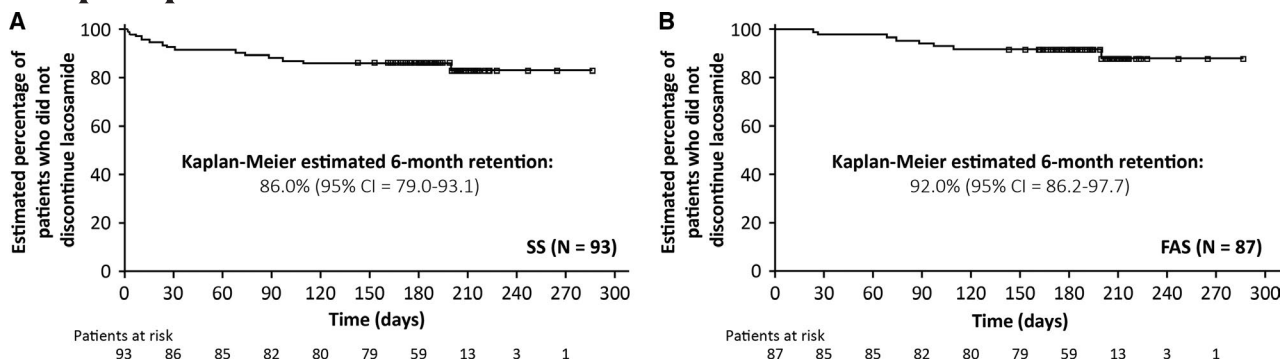
**FIGURE 2** Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) from baseline to month 6 (full analysis set [FAS]). For the month 6 assessment, data collected >135 days after baseline (visit 3) were used unless missing, in which case, data collected ≤135 days after baseline (visit 2) were used. Analyses were carried out in evaluable patients only. <sup>a</sup>Data for 11 patients in the FAS were missing. <sup>b</sup>Data for six patients in the FAS were missing

retrospective study in 403 patients with refractory epilepsy (80%).<sup>27</sup> The majority of patients (64.5%, FAS) reported a clinical improvement with the addition of lacosamide, as assessed by the PGIC. CGIC results were similar (64.2% improved), indicating that patients and physicians had a similar perception of change in condition. Post hoc analyses indicated that improvements in PGIC were similar in patients with confirmed low-grade glioma, and in patients with and without tumor treatment. The reported improvements in these metrics were similar to those observed in an open-label trial of lacosamide in patients with epilepsy (unrelated to brain tumors) receiving lacosamide as a later add-on (PGIC: 70.9% patients improved; CGIC: 73.1% improved).<sup>28</sup>

A lack of seizure control has been shown to have a negative impact on QoL in patients with epilepsy and low-grade gliomas.<sup>29</sup> However, despite the high seizure response rate and clinical improvements observed with lacosamide in our study, QoL (assessed by EQ-5D-5L) and symptom outcome measures (assessed by MDASI-BT) remained stable over a 6-month period. Numerous factors affect QoL in patients with BTRE, including brain tumor symptoms, brain tumor treatment, and a poor prognosis.<sup>18</sup> Patients may experience an increased symptom burden during and shortly after radiotherapy (early delayed radiation reaction), or as a result of systemic toxicities of chemotherapy. These changes in symptoms may negatively impact QoL and symptom outcome measures. Whereas in most patients tumor-related symptoms



**FIGURE 3** Post hoc analysis of Patient Global Impression of Change from baseline to month 6 (full analysis set [FAS]) in (A) a subgroup of patients with confirmed low-grade glioma (World Health Organization grade ≤ 2), and (B) subgroups of patients with and without tumor treatment. For the month 6 assessment, data collected >135 days after baseline (visit 3) were used unless missing, in which case, data collected ≤135 days after baseline (visit 2) were used. Analyses were carried out in evaluable patients only. Tumor treatment was defined as surgery or radiotherapy related to tumor within 90 days before/after first lacosamide dose, or concomitant chemotherapy treatment. <sup>a</sup>Nine patients had missing data. <sup>b</sup>Four patients had missing data. <sup>c</sup>Seven patients had missing data



**FIGURE 4** Kaplan-Meier estimated time to discontinuation of lacosamide from date of first dose in safety set (SS; A) and full analysis set (FAS; B). Patients who completed the study were censored at the date of last administration of lacosamide in the study or the study termination date if the date of the final lacosamide administration was not available. CI, confidence interval

would not be expected to change substantially over 6 months, in some cases tumor progression may have also negatively impacted symptom outcome measures and QoL. Data from a study in patients with high- and low-grade gliomas also showed stable QoL (assessed using the Patient-Weighted Quality of Life in Epilepsy Inventory-31 and the EORTC QLQ-C30) and good seizure control with add-on lacosamide; however, few patients (15/25) completed the follow-up assessments due to dropouts and disease progression in that study.<sup>18</sup>

Lacosamide was well tolerated by most patients with BTRE; the most common ADRs were vertigo, headache, nausea, and asthenia, in line with the adverse event profile reported with add-on lacosamide in adults with focal seizures.<sup>30-33</sup> Previous studies of lacosamide in patients with brain tumor-related epilepsy have also shown a favorable tolerability profile.<sup>15,16</sup> One of these studies was a retrospective chart review of data from 70 patients predominantly with

glioma, who were treated mainly with add-on lacosamide, which reported that 77% of patients had no toxicities.<sup>16</sup> Fatigue was the most common adverse event (6% of patients). In the other study, 87.3% of patients with gliomas (N = 71) did not report any toxicities with add-on lacosamide.<sup>15</sup> Dizziness was the most common treatment-emergent adverse event (5.7% of patients).

In contrast, studies in selected AEDs have highlighted safety concerns.<sup>7</sup> Phenytoin, lamotrigine, and carbamazepine are associated with allergic rash,<sup>34</sup> which is also a common side effect of chemotherapy. Certain AEDs including carbamazepine and valproic acid may induce or aggravate neutropenia and thrombocytopenia.<sup>35,36</sup> AEDs without enzyme-inhibiting or enzyme-inducing properties are favored for use in patients with BTRE, because the metabolism of chemotherapeutic agents could be altered when administered with concomitant enzyme inducers or inhibitors.<sup>2</sup> For example, valproate, an enzyme inhibitor, could increase the toxic effects of concomitantly administered chemotherapies.<sup>37</sup> Valproate is also known to modulate the immune system, with unclear effects.<sup>38</sup> Certain enzyme inducing or inhibiting AEDs, including carbamazepine, phenobarbital, phenytoin, and valproic acid, may also be associated with cognitive adverse events.<sup>2,29</sup>

A limitation of the current study is the lack of a control group of patients not receiving lacosamide. Furthermore, the observation period was relatively short, and the number of patients included was small. However, to the best of our knowledge this study represents the largest prospective investigation of the effectiveness and tolerability of lacosamide in patients with BTRE. It provides important data for this difficult-to-treat patient population in a clinical practice setting. The results suggest that add-on lacosamide is effective and generally well tolerated in patients with BTRE. These data, together with the low potential of lacosamide for drug-drug interactions and lack of enzyme induction or inhibition,<sup>39</sup> suggest that lacosamide is a suitable treatment option for patients with BTRE.

**TABLE 2** Adverse Drug Reactions (ADRs)

	Safety set, N = 93
Any ADR, n (%) <sup>a</sup>	15 (16.1)
Serious ADRs	1 (1.1)
Nonserious ADRs	14 (15.1)
ADRs leading to discontinuation	4 (4.3)
ADRs leading to death	0
Most common ADRs (≥2% of patients), n (%) <sup>a,b</sup>	
Vertigo	5 (5.4)
Headache	3 (3.2)
Nausea	3 (3.2)
Asthenia	2 (2.2)

<sup>a</sup>n (%) is the number and percentage of patients.

<sup>b</sup>MedDRA (Medical Dictionary for Regulatory Activities, v20.1) preferred term.



## ACKNOWLEDGMENTS

The authors thank the patients and their caregivers in addition to the investigators and their teams who contributed to this study (a full list of participating investigators is included in Appendix S1). This study was funded by UCB Pharma. Publication management was provided by Fabien Debailleul, PhD (UCB Pharma, Brussels, Belgium). Writing assistance was provided by Jayna Patel, PhD (Evidence Scientific Solutions, Horsham, UK), and was funded by UCB Pharma.

## CONFLICT OF INTEREST

R.R. has received support from and/or has served as a paid consultant for UCB Pharma (advisory board fees). M.M. has received support from and/or has served as a paid consultant for Eisai and UCB Pharma (advisory board fees, travel support, pharmaceutical industry-sponsored symposia, and research grants). M.G. has received support from and/or has served as a paid consultant for UCB Pharma. R.G. has received support from and/or has served as a paid consultant for UCB Pharma (consultancy fees and research support). M.D.B., L.J., and I.L. are employees of UCB Pharma. S.H. was contracted by UCB Pharma for statistical services. J.C. was an employee of UCB Pharma during the study, and is now an employee of Freeline Therapeutics. The remaining authors (C.H. and J.C.R.) have no conflicts of interest. 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.

## DATA AVAILABILITY STATEMENT

Data from noninterventional studies are outside of UCB Pharma's data sharing policy.

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## SUPPORTING INFORMATION

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

**How to cite this article:** Rudà R, Houillier C, Maschio M, et al. Effectiveness and tolerability of lacosamide as add-on therapy in patients with brain tumor-related epilepsy: Results from a prospective, noninterventional study in European clinical practice (VIBES). *Epilepsia.* 2020;61:647–656. <https://doi.org/10.1111/epi.16486>