FULL-LENGTH ORIGINAL RESEARCH

Conversion to lacosamide monotherapy in the treatment of focal epilepsy: Results from a historical-controlled, multicenter, double-blind study

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Summary

Objective: **To evaluate the efficacy and safety of conversion to lacosamide 400 mg/day monotherapy in adults with focal epilepsy.**

Methods: **This historical-controlled, double-blind study (NCT00520741) enrolled patients aged 16–70 years on stable doses of 1–2 antiepileptic drugs (AEDs) and experiencing 2–40 partial-onset seizures per 28 days during the 8-week prospective Baseline. Patients were randomized to lacosamide 400 or 300 mg/day (3:1 ratio), starting at 200 mg/day and titrated over 3 weeks to randomized dose. Patients then withdrew background AEDs over 6 weeks and entered a 10-week Monotherapy Phase. The primary assessment was the Kaplan-Meier–predicted percentage of patients on 400 mg/day in the full analysis set (FAS) meeting ≥1 predefined seizure-related exit criterion by day 112, compared with the historical-control threshold (65.3%).**

Results: **Four hundred twenty-five patients were enrolled and were eligible for safety analyses (400 mg/day, n = 319; 300 mg/day, n = 106). A total of 271 (63.8%) of 425 patients completed the Lacosamide Maintenance Phase (combined AED Withdrawal and Monotherapy Phases). Among 284 patients in the 400 mg/day group in the FAS, 82 (28.9%) met ≥1 exit criterion; the Kaplan-Meier–predicted exit percentage at day 112 for 400 mg/day (30.0%; 95% confidence interval [CI] 24.6–35.5%) was lower than the historical control. When exit events, withdrawal due to treatment-emergent adverse events (TEAEs), and withdrawal due to lack of efficacy were summed (n = 90), the predicted exit percentage (32.3%; 95% CI 26.8–37.8%) was also lower than the historical control. Most patients receiving 400 mg/day reported some improvement on the Clinical Global Impression of Change (75.4%) and Patient Global Impression of Change (74.3%). Overall, the most common (>10%) TEAEs were dizziness (24.0%), headache (14.4%), nausea (13.4%), convulsion (11.5%), somnolence (10.4%), and fatigue (10.1%); most (74.1%) were mild-to-moderate in intensity. Seventy-two patients (16.9%) discontinued due to TEAEs. Seventeen patients (4%, all receiving 400 mg/day) experienced serious AEs.**

Significance: **Lacosamide 400 mg/day monotherapy was effective, with a favorable safety profile in patients with focal epilepsy.**

KEY WORDS: **Monotherapy, Historical control, Lacosamide, Partial-onset seizures, Focal epilepsy.**

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The use of monotherapy for the treatment of seizures in epilepsy has a number of potential benefits over polytherapy including reduced likelihood of adverse events (AEs), improved adherence, decreased risk of drug–drug interactions and, possibly, lower medication costs.[1] Although the majority of patients with epilepsy can achieve seizure freedom with monotherapy,[2] only four of the newer antiepileptic drugs (AEDs) are approved in the United States as monotherapy (felbamate, lamotrigine, oxcarbazepine, and topiramate), and only oxcarbazepine and topiramate have an indication for initial monotherapy.[3–6]

It is challenging to demonstrate monotherapy efficacy in epilepsy clinical studies. The European Medicines Agency (EMA) accepts studies that demonstrate noninferiority to an AED with established use as monotherapy. However, the U.S. Food and Drug Administration (FDA) does not, because of concerns that both AEDs could be equally ineffective.[7] Monotherapy studies demonstrating superiority to placebo raise ethical concerns about morbidity risk when there are effective alternatives available to patients.[8,9] A conversion to monotherapy study design using a known effective agent administered at a subtherapeutic or minimally therapeutic dose (low-dose active control, also referenced in some studies as "pseudo-placebo") was used in previous epilepsy studies,[10,11] but is inconsistent with the Declaration of Helsinki[9] and is no longer considered ethical by the epilepsy community.

The FDA and the epilepsy community have agreed that future monotherapy trials should compare AEDs to a historical-control group based on the pooled "low-dose active control" groups from past conversion-to-monotherapy trials.[7,11] Eight similarly designed studies, incorporating a low-dose active control group were included in a meta-analysis, which established an expected exit percentage (proportion of patients who met predefined exit criteria) of 85.1% with a lower bound of the 95% prediction interval of 65.3%.[11] Superiority over the historical controls can be declared if the upper limit of the 95% confidence interval (CI) for the study drug is less than the lower limit of the prediction interval for the prespecified historical-control exit percentage (65.3%). Study design, recruitment criteria, and population characteristics for future studies are required to be as similar as possible to the studies constituting the historical control. Such historical-controlled monotherapy trials still require inclusion of two effective-dose study arms to maintain study design integrity, including randomization and blinding of treatment assignment. Although a randomized concurrent controlled trial offers a higher class of evidence, the historical-control trial design is currently the only AED study design acceptable to the FDA to achieve an indication for monotherapy.

Four AEDs have recently been evaluated as conversion to monotherapy using the historical-control study design: lamotrigine extended-release,[12] levetiracetam extended-release,[13] pregabalin,[14] and eslicarbazepine.[15,16]

We report the results of a historical-control study (A Lacosamide EXchange to Monotherapy Trial [ALEX-MT]) to assess the efficacy and safety of conversion to lacosamide monotherapy, an AED that is approved for the adjunctive treatment of partial-onset seizures (POS) in adults.[17–19]

Methods

Study design

This study (SP902; Clinicaltrials.gov: NCT00520741) was a historical-controlled, multicenter, double-blind, conversion to monotherapy study conducted between August 2007 and December 2012 in the United States, Canada, Europe, and Australia. Prior approval was received from the appropriate institutional review body for each center, and written informed consent was obtained from each patient. This study was conducted in accordance with the Good Clinical Practice requirements, the Declaration of Helsinki, and local laws.

Following an 8-week prospective Baseline Phase, patients were randomized in a blinded fashion in a 3:1 ratio to lacosamide 400 or 300 mg/day (Fig. S1). Treatment allocation was generated by an Interactive Voice Response System based on a central randomization scheme, stratified by region (U.S.A./Canada and other regions), which assigned the applicable kit number. A 300 mg/day treatment arm was included to blind the treatment group and to ensure a study design consistent with the historical-control studies.

Lacosamide was administered as 50 or 100 mg tablets, identical in appearance. An identical placebo tablet was incorporated in the 300 mg/day dose group from the final week of titration to maintain blinding throughout the study. During the 3-week Titration Phase, lacosamide was initiated at a dose of 200 mg/day (100 mg/day twice daily [b.i.d.]), and titrated by 100 mg/day each week to the randomized dose (300 or 400 mg/day). Patients then entered the 16-week Lacosamide Maintenance Phase, which included a 6-week background AED Withdrawal Phase and a 10-week lacosamide Monotherapy Phase. Background AEDs were tapered in approximately equal decrements every 2 weeks. The second background AED, if present, was withdrawn on day 1 of the AED Withdrawal Phase. After the AED Withdrawal Phase, patients were maintained on lacosamide monotherapy at the randomized dose (a single reduction in dose was permitted during the Lacosamide Maintenance Phase for reasons of tolerability). The study had predefined exit criteria consistent with the historical-control design. Patients who met the exit criteria or completed the 10-week Monotherapy Phase could then taper their lacosamide dose, initiate therapy with commercial lacosamide, or transition to the open-label extension study (SP904; Clinicaltrials.gov: NCT00530855). Patients who prematurely discontinued the study and were not considered exits were not eligible to

transition to the open-label extension study. Safety follow-up lasted for 2 weeks after last dose for those who tapered off study medication.

Key inclusion criteria

Male and female patients aged 16–70 years with a diagnosis of epilepsy with POS, and electroencephalography (EEG) and brain computerized tomography (CT) scan or magnetic resonance imaging (MRI) evaluation consistent with this diagnosis, were enrolled in the study. This study used the International Classification of Epileptic Seizures, 1981.[20] Patients with simple POS (with motor signs) or complex POS (with or without secondary generalization) were required to have a seizure frequency of 2–40 per 28 days during the 8-week Baseline Phase. A stable dose of one or two marketed AEDs for at least 28 days was required prior to Baseline and during the Baseline Phase. The dosage of the second AED was required to be ≤50% of the minimum recommended maintenance dose per United States product label.

Key exclusion criteria

Patients were excluded if they had a history of primary generalized epilepsy, status epilepticus within the previous year, cluster seizures within 8 weeks of study start, any seizure-free period lasting 28 days or longer during the Baseline Phase, or >5 seizures of any type in a single day during the Baseline Phase. Additional exclusion criteria included any history of conversion disorders or other nonepileptic ictal events. Patients were also excluded from entering the study if they had an implanted vagus nerve stimulator, or had received benzodiazepines, phenobarbital, or primidone, or were regularly receiving neuroleptics, monoamine oxidase inhibitors, barbiturates, or narcotic analgesics within 28 days of study entry or during the Baseline Phase.

Assessments

The primary efficacy assessment was the percentage of patients in the full analysis set (FAS) receiving lacosamide 400 mg/day who met one or more of the following predefined exit criteria[11] by day 112 of the Lacosamide Maintenance Phase (end of Lacosamide Maintenance Phase):

1. A twofold or greater increase in average monthly (28-day) POS frequency (motor and nonmotor) compared with average monthly POS frequency (motor and nonmotor) during the Baseline Phase.
2. A twofold or greater increase in consecutive 2-day POS frequency (motor and nonmotor) versus the highest consecutive 2-day POS frequency (motor and nonmotor) that occurred during the Baseline Phase. If the highest consecutive 2-day POS frequency during the Baseline Phase was 1, a 2-day POS frequency of ≥3 was required to meet this exit criterion.
3. Occurrence of a single generalized tonic–clonic seizure (GTCS) if none had occurred in the 6 months prior to randomization.
4. A prolongation or worsening of overall seizure duration, frequency, type, or pattern considered by the investigator as serious enough to warrant study discontinuation.
5. Status epilepticus or new onset of serial/cluster seizures.

Secondary efficacy assessments included the time to first occurrence of any exit event; the sum of exit event percentage, percentage of withdrawals due to AEs, percentage of withdrawals due to lack of efficacy (400 mg/day group only); and duration of monotherapy treatment (days) during the Monotherapy Phase. In addition, Clinical Global Impression of Change (CGIC) and Patient's Global Impression of Change (PGIC) were assessed at study termination or completion. Exploratory efficacy analyses were also performed on the 300 mg/day dose group. Post hoc analyses on seizure frequency and seizure freedom were assessed for both the 300 and 400 mg/day dose groups.

Safety assessments included incidence of treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and withdrawal due to AEs. Other assessments included: hematology, blood chemistry, and urinalysis parameters; 12-lead electrocardiography (ECG) studies; vital sign measurements (i.e., blood pressure, pulse rate); physical and neurologic examination findings; and body weight.

Statistical analysis

The primary analysis of the study compared the 400 mg/day dose group with the historical low-dose active control group.[11] The study was not randomized for the primary outcome. Patients were randomized 3:1 to one of two therapeutic doses of lacosamide 400 or 300 mg/day, to ensure a study design comparable to the historical control.

A sample size of 338 enrolled patients in the lacosamide 400 mg/day group was calculated to provide approximately 90% power for the comparison of the Kaplan-Meier estimate of the percentage of patients exiting by day 112 versus the historical-control exit percentage (65.3%). This sample size calculation was based on a one-sided 0.025 significance level, an assumed 55% exit percentage, a 20% dropout percentage during the Titration Phase, and a 10% dropout percentage during the Lacosamide Maintenance Phase for nonexit criteria reasons.

For calculation of the Kaplan-Meier estimate, the date of the earliest exit was used in the event of a patient meeting more than one exit criterion. Patients who withdrew for nonexit criteria reasons were censored as of the date of the last Lacosamide Maintenance Phase dose. Lacosamide 400 mg/day would be declared an effective withdrawal to monotherapy treatment if the upper limit of the 95% CI for the predicted exit estimate was less than the lower limit of the 95% prediction interval for the prespecified historical-control exit percentage (65.3%). The Kaplan-Meier plot of the time to exit was calculated for time to first occurrence of any exit

event. As exploratory analyses, results of the efficacy of the 300 mg/day dose group are descriptive only. Sensitivity analyses were performed on the primary efficacy assessment using a Cox proportional hazards model to measure the effects of baseline characteristics, including age, gender, racial group, region, use of oxcarbazepine/carbamazepine, and the log-transformed baseline seizure frequency. Post hoc analyses included 50% and 75% responder rates (the proportion of patients who experienced a ≥50% and ≥75% reduction in seizure frequency per 28 days compared with baseline) as well as increase in seizure frequency of ≥25% from baseline, and patients achieving seizure freedom during the 10-week Monotherapy Phase.

Efficacy assessments were evaluated using the FAS (patients who completed the Titration Phase and started withdrawing background AEDs). Safety assessments were evaluated using the Safety Set (SS; all patients who received at least one dose of lacosamide). Post hoc analyses were performed on the SS and a subset of patients in the FAS who completed the Monotherapy Phase.

Results

A total of 425 patients were enrolled and included in the safety analyses, and 383 were included in the efficacy analyses. Overall, 271 patients (63.8%) completed the Lacosamide Maintenance Phase (Fig. 1). Dropout rates from the 400 mg/day group during the Titration Phase (11.0%) and Lacosamide Maintenance Phase (6.7%) for nonexit criteria were lower than was projected in the sample size calculation (20% and 10%, respectively), hence the study remained adequately powered. Patient characteristics were generally comparable between treatment groups (Table 1) and similar to those that are available for the historical-control studies, including regional distribution. Patients were slightly older in the current study (mean age 40.6 years compared with 35–38 years in the historical control), and fewer patients took carbamazepine or oxcarbazepine as a primary or secondary background AED (n = 146; 34.4%), compared with 46–64% in the historical-control studies.[11] The proportion of patients with a history of GTCS was at the high end of the range reported in the historical-control studies (67.5% vs. 19–71%).[21–25]

Primary assessment

Among 284 patients in the lacosamide 400 mg/day group in the FAS, 82 (28.9%) met at least one exit criterion (Table 2). The Kaplan-Meier estimate of the percentage of patients in the 400 mg/day group meeting at least one exit criterion by day 112 was 30.0% (95% CI 24.6–35.5%; Fig. 2). Superiority over the historical control was demonstrated, as the upper limit of the two-sided 95% CI for this estimate (35.5%) was lower than the historical-control exit percentage (65.3%; Fig. 2).

Secondary assessments

The mean (± standard deviation, SD) time to exit due to meeting at least one exit criterion during the Lacosamide Maintenance Phase was 45.0 ± 24.3 days (n = 284) in the lacosamide 400 mg/day group. If all predefined seizure-related exits, withdrawals due to an AE, and withdrawals due to lack of efficacy were counted as exit events, 90 patients (31.7%) exited; the Kaplan-Meier predicted exit percentage at day 112 was 32.3% (95% CI 26.8–37.8%).

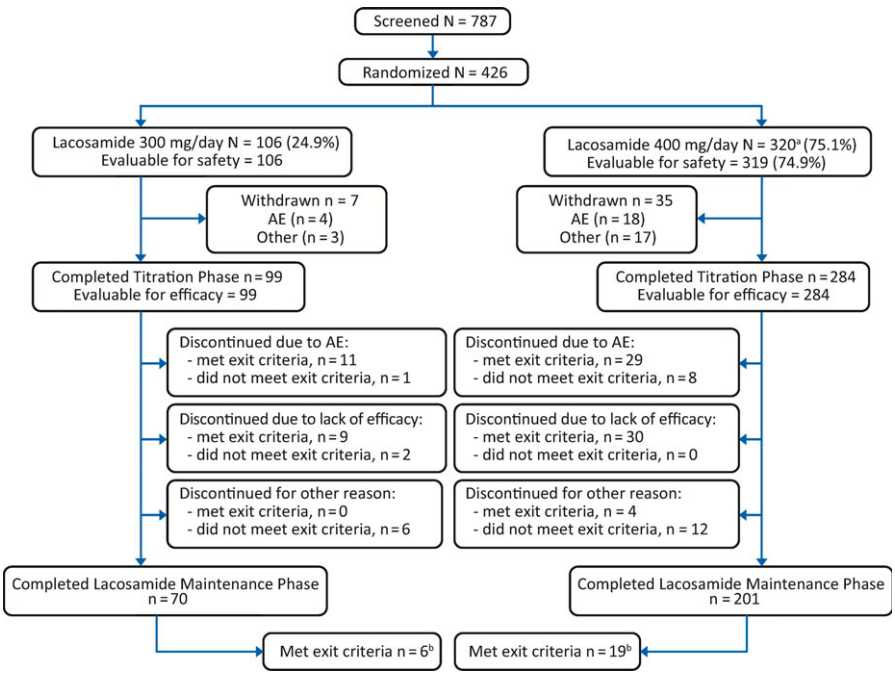

Figure 1.
Patient disposition. [a]One patient was randomized at two centers. This patient was summarized once in the Enrolled Set and removed from the Safety Set. [b]Patients who completed the Lacosamide Maintenance Phase but an exit was discovered using a more conservative computational algorithm than that used by the investigator. AE, adverse event.

Table 1. Patient baseline demographics and epilepsy characteristics

	Safety set			Full analysis set		
	Lacosamide 400 mg/day (N = 319)	Lacosamide 300 mg/day (N = 106)	All patients (N = 425)	Lacosamide 400 mg/day (N = 284)	Lacosamide 300 mg/day (N = 99)	All patients (N = 383)
Age, years						
Mean (SD)	40.4 (12.5)	41.4 (14.3)	40.6 (13.0)	40.1 (12.6)	41.4 (14.2)	40.4 (13.1)
Range	16–69	17–69	16–69	16–69	17–69	16–69
Gender						
Male, n (%)	150 (47.0)	56 (52.8)	206 (48.5)	136 (47.9)	54 (54.5)	190 (49.6)
Race						
Black, n (%)	53 (16.6)	9 (8.5)	62 (14.6)	48 (16.9)	8 (8.1)	56 (14.6)
White, n (%)	246 (77.1)	91 (85.8)	337 (79.3)	219 (77.1)	85 (85.9)	304 (79.4)
Other, n (%)	20 (6.3)	6 (5.7)	26 (6.1)	17 (6.0)	6 (6.1)	23 (6.0)
Country						
U.S.A.	249 (78.1)	82 (77.4)	331 (77.9)	223 (78.5)	75 (75.8)	298 (77.8)
All other countries	70 (21.9)	24 (22.6)	94 (22.1)	61 (21.5)	24 (24.2)	85 (22.2)
BMI, kg/m^2						
Mean (SD)	28.7 (6.6)	28.2 (5.7)	28.6 (6.4)	28.9 (6.7)	28.2 (5.8)	28.7 (6.5)
Time since first diagnosis (years), mean (SD)	16.9 (13.5)	18.0 (15.3)	17.2 (14.0)	16.6 (12.9)	18.3 (14.9)	17.1 (13.5)
Baseline seizure frequency per 28 days, median (range)	6.50 (2.0–39.0)	7.00 (2.0–40.0)	6.62 (2.0–40.0)	6.50 (2.0–39.0)	7.00 (2.0–40.0)	6.50 (2.0–40.0)
Seizure history, n (%)						
Simple partial	155 (48.6)	46 (43.4)	201 (47.3)	139 (48.9)	43 (43.4)	182 (47.5)
Complex partial	273 (85.6)	90 (84.9)	363 (85.4)	244 (85.9)	87 (87.9)	331 (86.4)
Secondary generalized	223 (69.9)	64 (60.4)	287 (67.5)	197 (69.4)	59 (59.6)	256 (66.8)
Seizure clusters >8 weeks before baseline	7 (2.2)	3 (2.8)	10 (2.4)	6 (2.1)	3 (3.0)	9 (2.3)
Status epilepticus >12 months before baseline	4 (1.3)	2 (1.9)	6 (1.4)	3 (1.1)	2 (2.0)	5 (1.3)
Secondary GTCS within 4 months of baseline	149 (46.7)	41 (38.7)	190 (44.7)	130 (45.8)	37 (37.4)	167 (43.6)
AEDs discontinued prior to study entry						
≤2	175 (54.9)	55 (51.9)	230 (54.1)	160 (56.3)	49 (49.5)	209 (54.6)
≥3	144 (45.1)	51 (48.1)	195 (45.9)	124 (43.7)	50 (50.5)	174 (45.4)
Number of background AEDs						
1	236 (74.0)	76 (71.7)	312 (73.4)	210 (73.9)	69 (69.7)	279 (72.8)
2	83 (26.0)	30 (28.3)	113 (26.6)	74 (26.1)	30 (30.3)	104 (27.2)
Primary background AED						
Levetiracetam	72 (22.6)	22 (20.8)	94 (22.1)	65 (22.9)	22 (22.2)	87 (22.7)
Carbamazepine	65 (20.4)	21 (19.8)	86 (20.2)	57 (20.1)	18 (18.2)	75 (19.6)
Lamotrigine	46 (14.4)	14 (13.2)	60 (14.1)	43 (15.1)	14 (14.1)	57 (14.9)
Phenytoin	40 (12.5)	14 (13.2)	54 (12.7)	36 (12.7)	11 (11.1)	47 (12.3)
Valproate	33 (10.3)	11 (10.4)	44 (10.4)	25 (8.8)	10 (10.1)	35 (9.1)
Oxcarbazepine (OXC)	25 (7.8)	13 (12.3)	38 (8.9)	24 (8.5)	13 (13.1)	37 (9.7)
Topiramate	24 (7.5)	3 (2.8)	27 (6.4)	22 (7.7)	3 (3.0)	25 (6.5)
Use of carbamazepine or oxcarbazepine (as primary or secondary background AED)	104 (32.6)	42 (39.6)	146 (34.4)	94 (33.1)	39 (39.4)	133 (34.7)

AED, antiepileptic drug; BMI, body mass index; GTCS, generalized tonic–clonic seizure; SD, standard deviation.

The upper limit of the two-sided 95% CI for this estimate (37.8%) was lower than the historical-control exit percentage (65.3%) and was consistent with the primary efficacy analysis (Fig. 2). Median duration of monotherapy treatment in the 400 mg/day group during the Monotherapy Phase was 71.0 days (range 2–105). The proportion of patients receiving 400 mg/day who showed some improvement was 75.4% on the CGIC and 74.3% on the PGIC. Of these, 19.7% and 28.5%, respectively, were rated as very much improved; 40.8% and 32.7%, respectively, were rated as much improved; and 14.8% and 13.0%, respectively, were rated as minimally improved. Similarly, most patients in the 300 mg/day group were rated as improved on the CGIC and PGIC (72.7% for both; Fig. S2).

Table 2. Incidence of exit criteria and predicted exit percentage, FAS

Lacosamide maintenance phase	Primary efficacy analysis lacosamide 400 mg/day N = 284 n (%)	Exploratory analysis lacosamide 300 mg/day N = 99 n (%)
Patients meeting at least one exit criterion (patients can be counted under more than one exit criterion)	82 (28.9)	26 (26.3)
Exit 1: At least a twofold increase in POS frequency seizures per 28 days compared with the baseline phase	50 (17.6)	14 (14.1)
Exit 2: At least a twofold increase in consecutive 2-day POS frequency compared with the baseline phase	34 (12.0)	10 (10.1)
Exit 3: Occurrence of a GTCS if none had occurred in the 6 months prior to randomization	9 (3.2)	4 (4.0)
Exit 4: Prolongation or worsening overall seizure duration, frequency, type, or pattern that necessitated study discontinuation	23 (8.1)	8 (8.1)
Exit 5: Status epilepticus or new onset of serial/cluster seizures	5 (1.8)	1 (1.0)
Kaplan-Meier predicted exit percentage at day 112 (95% CI)	30.0 (24.6, 35.5)	27.3 (18.4,36.3)
Historical-control exit percentage, lower bound for the 95% prediction interval	65.3	65.3

POS, partial-onset seizures; FAS, full analysis set; GTCS, generalized tonic–clonic seizures; CI, confidence interval.

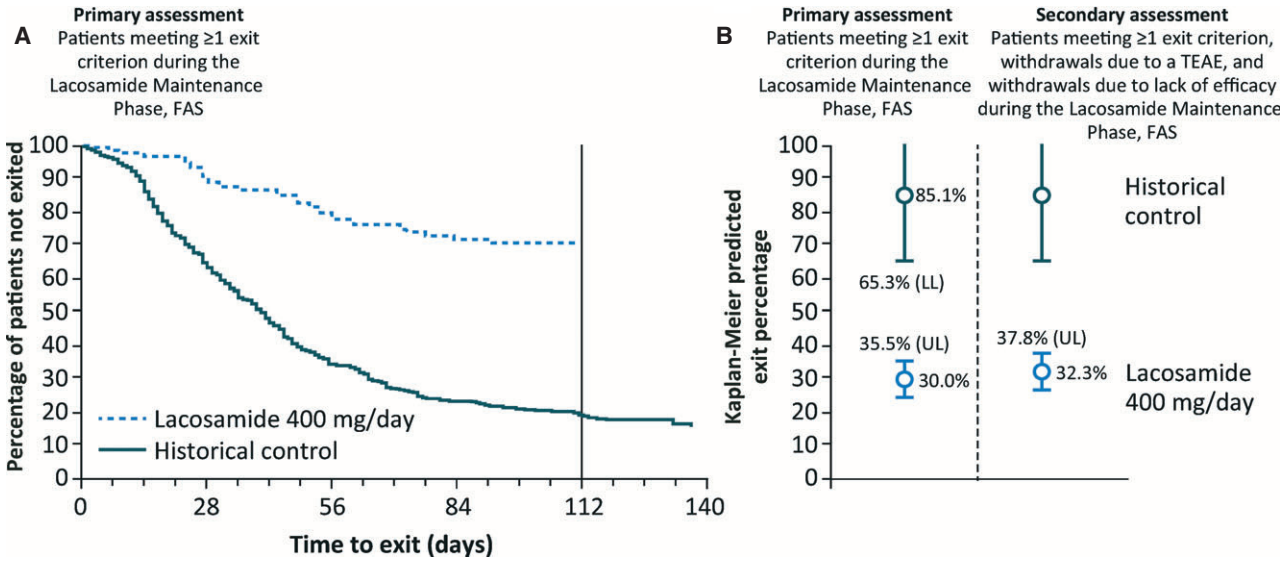

Figure 2.
Kaplan-Meier predicted time to exit due to meeting at least one exit criterion during the Lacosamide Maintenance Phase, 400 mg/day group and historical control[11] (**A**) Kaplan-Meier predicted exit percentages for the lacosamide 400 mg/day group compared with historical control[11] and percentage of patients meeting ≥1 exit criterion, withdrawal due to a TEAE, and withdrawal due to lack of efficacy in the Lacosamide Maintenance Phase, FAS (**B**) TEAE, treatment emergent-adverse event; FAS, full analysis set; LL, lower limit; UL, upper limit.

Exploratory analyses

When the primary assessment was adjusted for baseline characteristics, the Kaplan-Meier predicted exit percentage in the 400 mg/day group was 29.2% (95% CI 23.5–34.5%).

In patients who received lacosamide 300 mg/day, 26 patients (26.3%) met at least one exit criterion. The Kaplan-Meier estimate was 27.3% (95% CI 18.4–36.3%) and the upper limit of the two-sided 95% CI for this estimate (36.3%) was lower than the lower limit of the historical-control exit percentage (65.3%). The mean (±SD) time to exit due to meeting at least one exit criterion during the Lacosamide Maintenance Phase was 37.4 ± 21.2 days in the 300 mg/day group. Median duration of monotherapy treatment in the 300 mg/day group during the Monotherapy Phase was 71.0 days (range 1–100).

Analysis by baseline subgroup showed that the subgroup of patients from North America had a lower percentage of subjects meeting at least 1 exit criterion (26.9% [63/234])

compared with all other regions (38.0% [19/50]). Similarly, the exit percentage in the U.S.-only subgroup was lower compared with all other countries (26.9% [60/223] vs. 36.1% [22/61]). Interpretation of these results should take into account that a large majority of subjects were from the U.S. region (223 vs. 61).

Post hoc analyses

In the 400 mg/day group, 133/319 patients (41.7%) in the SS and 122/201 (60.7%) of those who completed the Monotherapy Phase had a ≥50% reduction in seizure frequency during the 10-week Monotherapy Phase compared with Baseline (Fig. 3). A ≥75% reduction in seizure frequency during the Monotherapy Phase compared with baseline was seen in 77/319 (24.1%) of the SS and in 69/201 (34.3%) patients who completed the Monotherapy Phase. Thirty (14.9%) of 201 patients receiving 400 mg/day who completed the Monotherapy Phase remained seizure-free during the Monotherapy Phase (Fig. 3). In the 400 mg/day group, an increase in seizure frequency of ≥25% was seen in 48/319 patients (15.0%) in the SS and 16/201 (8.0%) who completed the Monotherapy Phase. The proportion of patients in the 300 mg/day group with ≥50% or ≥75% reduction in seizure frequency or who became seizure-free was comparable to that seen in the 400 mg/day group (Fig. 3).

Safety

A total of 359/425 patients (84.5%) reported a TEAE (defined as an AE with onset during the treatment period). The most common TEAEs in the overall population were dizziness (24.0%), headache (14.4%), nausea (13.4%), convulsion (11.5%), somnolence (10.4%), and fatigue (10.1%; Table 3). These TEAEs (with the exception of those coded to convulsion) were more common during the Titration Phase than during the Monotherapy Phase (Fig. S3). During the treatment period, 69 patients (16.2%) discontinued due to a TEAE; 72 patients (16.9%) discontinued due to an AE at any point during the study. The most common AEs leading to discontinuation during the treatment period were TEAEs coded to convulsion (8.2%), dizziness (1.6%), grand mal convulsion (1.2%), and nausea (0.9%). Forty-nine patients reported a TEAE coded to convulsion, 35 of whom discontinued the study; 32 of these met predefined exit criteria. There was no evidence for any effect of lacosamide treatment on vital signs, weight, ECG evaluations, or physical and neurologic examinations.

Seventeen patients (all in the 400 mg/day group) reported 19 SAEs during the treatment period. The only SAE in more than one patient was convulsion (n = 5). The majority of SAEs (12/19) were considered by the investigator not to be related to treatment.

Three patients died during the study, all in the 400 mg/day dose group. None of the deaths were considered to be related to lacosamide. One was a consequence of polytrauma, unrelated to epilepsy, and two were due to sudden unexpected death in epilepsy (SUDEP), one of which was probable and one definite. One SUDEP occurred during the AED Withdrawal Phase in a patient with a 9-year history of epilepsy, and the other in a patient with a 25-year history of epilepsy while transitioning to the open-label study. Both patients had a history of exclusively secondarily generalized seizures and had experienced fewer seizures during the Monotherapy Phase than during Baseline (0 vs. 3.5 and 20.2 vs. 32.5 per 28 days). Twenty-seven patients with exclusively GTCS were enrolled and two of these patients had SUDEP. Due to the potential increased risk of SUDEP in

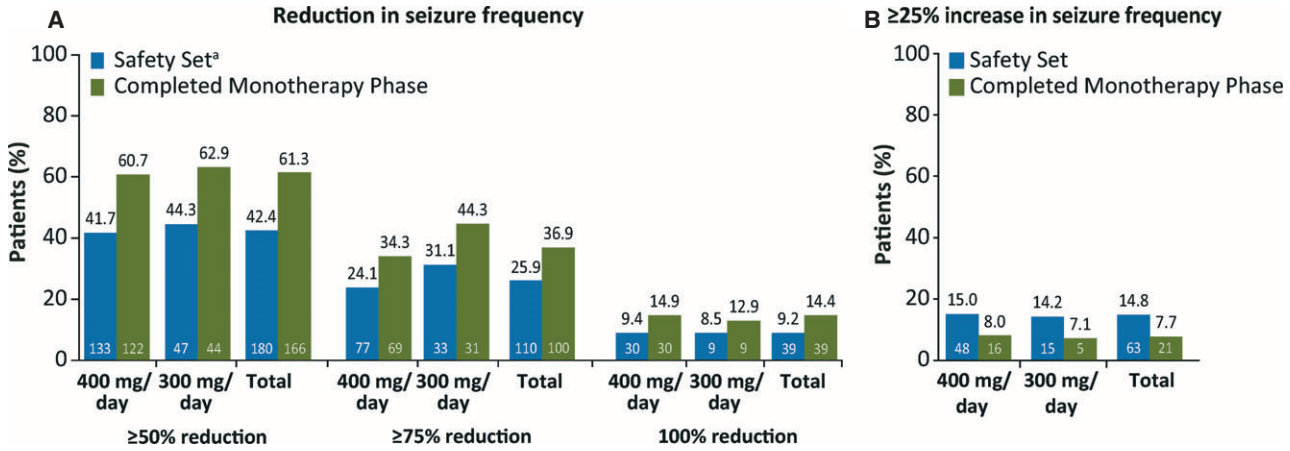

Figure 3.

Proportion of patients with ≥50%, ≥75%, and 100% (seizure-free) reduction (**A**) or ≥25% increase (**B**) in seizure frequency per 28 days during the 10-week Monotherapy Phase compared with Baseline Phase, safety set, and patients completing the Monotherapy Phase. [a]Patients who discontinued the study prior to the Monotherapy Phase or did not complete the Monotherapy Phase were considered to not be seizure-free.

Table 3. Incidence of TEAEs[a] of any causality with onset during any part of the treatment period, SS

	400 mg/day N = 319	300 mg/day N = 106	Total N = 425
Any TEAE, n (%)	272 (85.3)	87 (82.1)	359 (84.5)
Serious TEAE, n (%)	17 (5.3)	0	17 (4.0)
Discontinuations due to TEAE, n (%)	54 (16.9)	15 (14.2)	69 (16.2)
Deaths, n (%)	3 (0.9)	0	3 (0.7)
TEAEs occurring in >5% of patients			
Dizziness	83 (26.0)	19 (17.9)	102 (24.0)
Headache	42 (13.2)	19 (17.9)	61 (14.4)
Nausea	44 (13.8)	13 (12.3)	57 (13.4)
Convulsion[b]	32 (10.0)	17 (16.0)	49 (11.5)
Somnolence	29 (9.1)	15 (14.2)	44 (10.4)
Fatigue	32 (10.0)	11 (10.4)	43 (10.1)
Nasopharyngitis	25 (7.8)	7 (6.6)	32 (7.5)
Tremor	21 (6.6)	8 (7.5)	29 (6.8)
Diarrhea	21 (6.6)	7 (6.6)	28 (6.6)
Vision blurred	19 (6.0)	6 (5.7)	25 (5.9)
Insomnia	17 (5.3)	7 (6.6)	24 (5.6)
Vomiting	21 (6.6)	2 (1.9)	23 (5.4)

SS, safety set; TEAE, treatment-emergent adverse event.
[a]Coded using Medical Dictionary of Regulatory Activities (MedDRA), Version 9.1.
[b]Because the preferred term of convulsions captures both worsening of seizure conditions and improvements (emergence of less severe seizure types), the incidence of convulsion may be an overestimate of the number of patients with worsening seizures.

patients with exclusively GTCS in a study setting, the one remaining patient with only GTCS was withdrawn.

Discussion

This study, conducted in accordance with U.S. regulatory criteria, demonstrates the efficacy and safety of conversion to lacosamide 400 mg/day monotherapy in 16- to 70-year-old patients with focal epilepsy.

The primary efficacy variable was the percentage of patients meeting predefined exit criteria compared with historical controls. Patients treated with lacosamide 400 mg daily were significantly less likely to meet predefined exit criteria relative to an exit rate established from a historical low-dose active control group.[11]

A number of secondary analyses were performed, the findings of which supported the primary efficacy analysis of this study. A more conservative analysis including patients who discontinued the study for reasons other than meeting predefined seizure-related exit criteria (i.e., due to an AE or perceived lack of efficacy not severe enough to meet exit criteria) supported the efficacy of lacosamide as monotherapy. Even in this more conservative analysis, the upper limit of the 95% CI of the estimated exit percentage at day 112 in the lacosamide 400 mg/day group was substantially below the historical-control exit percentage (37.8% vs. 65.3%).

Lacosamide 300 mg/day, an established effective dose for adjunctive therapy, was included to maintain the study blind and to ensure a study design consistent with the historical-control studies. Its efficacy was assessed as exploratory analyses with findings that were similar to those for the 400 mg/day group.

The primary endpoint of this study differs from the seizure frequency-based endpoints used in most epilepsy studies. Additional information on patient outcomes is provided through CGIC and PGIC assessments, and post hoc analyses of responder rates and seizure freedom rates are included to provide a clinical context to the study results. The majority of physicians and patients in both dose groups reported at least some degree of subjective improvement based on CGIC and PGIC values. Post hoc analyses in the 400 mg/day group revealed that almost two thirds of patients who completed the Monotherapy Phase experienced a ≥50% reduction and one-third experienced a ≥75% reduction in seizure frequency per 28 days compared with Baseline.

The historical-control study design has several potential limitations: Patients were aware that they would receive one of two effective doses of lacosamide; the study duration was relatively short compared with actual clinical practice; the background AED Withdrawal Phase had a fixed duration; and patients were converted to monotherapy from a stable regimen of 1–2 AEDs. Although a randomized controlled trial offers a higher class of evidence, the historical-control trial design is the only currently acceptable design in the United States for establishing the efficacy and safety of AED monotherapy use.

Our study was designed to match the historical-control studies as much as possible with respect to overall design, patient population, exit criteria, and data analysis.[11] Patient demographics, including age, gender, race, nationality,

baseline seizure frequency, epilepsy type, and history in this study were generally similar to the data available for the historical-control studies (Table S1).[11] At the time the study was conducted (2007–2012), patients were treated with a greater variety of AEDs than when the historical-control studies were conducted due to the availability of a greater number of new therapies. Levetiracetam was the most common background AED in this study. Although carbamazepine was the second most common background AED, its use was lower than in the historical-control studies.

The safety profile of lacosamide reported in the present study is generally similar to that observed in lacosamide adjunctive therapy studies.[17–19] The most frequently reported TEAEs included dizziness, nausea, and headache. Analysis by study phase revealed that the incidence of TEAEs was higher during the Titration Phase of the study while patients were still receiving background AEDs and thus may have been related to polytherapy, the higher initial lacosamide dose of 200 mg/day, and fixed titration to the randomized dose. Most TEAEs (with the exception of events coded to convulsions) occurred less frequently during the Monotherapy Phase and rarely led to discontinuation. In clinical settings that are not constrained by the limitations of the historical-control design, more flexible titration schedules may be expected to reduce the incidence of AEs.

Reporting of terms coded to convulsions was higher during the Monotherapy Phase than during the Titration Phase, but patients did not necessarily have GTCS or consistently meet predefined exit criteria. In this study, all changes of seizure type or severity were coded to convulsions, even the onset of a new milder seizure type despite resolution of more severe seizures.

Seizures are a cardinal manifestation of epilepsy. Any change in AED regimen may engender risk of seizure exacerbation, and a proportion of patients may be expected to experience worsening seizures when current therapy is withdrawn.[26,27] Nonetheless, all patients entering this study had suboptimal seizure control that warranted a change in treatment. It is not possible to assess how many of these patients would have experienced a deterioration of seizure control regardless of intervention given the highly variable natural course of epilepsy.[28] The constraints imposed by the historical-control design of this study did not allow for individualized and flexible conversion to monotherapy options that would be utilized in clinical settings.

There were two cases of SUDEP in this study, both in patients with a history of exclusively GTCS. SUDEP has been reported in clinical trials of adjunctive antiepileptic therapy in patients with refractory seizures,[29] as well as in conversion-to-monotherapy trials.[14] A causal relationship between SUDEP and the administration of AEDs has not been established.[30] The most important known risk factor for SUDEP is the occurrence and frequency of GTCS.[31] Hence, control of GTCS remains the most important clinical intervention to reduce the risk of SUDEP.

In addition to meeting regulatory guidelines, this study suggests a potential positive impact on clinically relevant outcomes. CGIC and PGIC ratings and post hoc analyses of responder rates and the seizure freedom rate indicate that most patients whose seizures were not controlled on their existing treatment improved when converted to lacosamide monotherapy. It should be noted that although the patients in this study had epilepsy that was somewhat more drug resistant than would usually be considered for monotherapy in clinical practice (45.4% of patients having failed ≥3 previous AEDs and a high proportion of patients had a history of GTCS), patients with less drug-resistant epilepsy may also benefit from lacosamide monotherapy. In addition, lacosamide may be better tolerated in clinical practice, where flexible titration schedules may allow physicians to withdraw existing treatment at a rate adjusted for optimal efficacy and tolerability.

In conclusion, the use of lacosamide 400 mg daily, divided b.i.d., was demonstrated to be effective as monotherapy for the treatment of adult patients with focal epilepsy with a favorable safety profile. The results of this study also suggest that lacosamide has a positive impact on clinically relevant measures, and is a well-tolerated alternative for conversion to monotherapy in patients with uncontrolled focal epilepsy. Further exploratory analysis on relevant endpoints, such as whether there are certain patient characteristics that could predict those more likely to have efficacy or side effects from lacosamide treatment, could be conducted in the future to clinically contextualize the results of this study.

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Conflict of Interest

Dr Wechsler has acted as a consultant or served on advisory boards for Cyberonics, Eisai, Upsher-Smith, Sunovion, Acorda, Lundbeck, Gerson, Lehrman Group Inc, and UCB Pharma and is on Speaker's Bureaus for Cyberonics, Sunovion, Eisai, Lundbeck, and UCB Pharma. Dr Li has acted as a consultant or served on advisory boards for Sunovion and received financial support for research from Sunovion, UCB Pharma, and Upsher-Smith. Dr French has acted as a consultant or received financial support for research from Acorda, Eisai Medical Research, GlaxoSmithKline, Impax, Johnson & Johnson, Mapp Pharmaceuticals, Marinus, Novartis, Lundbeck, Pfizer, Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Pharma, Upsher-Smith, and Vertex. Dr O'Brien has acted as a consultant or served on advisory boards for UCB Pharma and SciGen and has

received financial support for research from Neurotherapeutics Pharma, Eisai, UCB Pharma, and Velacor. Drs D'Cruz, Goodson, and Brock, and Ms Williams are employees of UCB Pharma. 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.

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Appendix I

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design.

Figure S2. Clinical Global Impression of Change (A) and Patient's Global Impression of Change during the lacosamide maintenance phase (B), FAS.

Figure S3. Incidence of most frequently reported TEAEs (>10%) by study phase in the total population, SS.

Table S1. Baseline characteristics in the trials included in the historical control.