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Efficacy and safety of lacosamide as first add-on or later adjunctive treatment for uncontrolled partial-onset seizures: A multicentre open-label trial

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ABSTRACT

Purpose: To evaluate the efficacy and safety of lacosamide administered as either first add-on or later add-on antiepileptic drug (AED) therapy for patients with uncontrolled partial-onset seizures (POS).
Methods: In this open-label, multicentre trial, patients with POS initiated oral lacosamide (titrated to 400 mg/day) either as add-on to first AED monotherapy, or as later add-on to 1–3 concomitant AEDs after ≥2 previous AEDs. The primary efficacy variable was the proportion of patients achieving seizure freedom for the first 12 weeks of the 24-week Maintenance Phase.
Results: 456 patients received ≥1 dose of lacosamide (96 as first add-on, 360 as later add-on). In the first add-on cohort, 27/72 (37.5%) patients completed 12 weeks treatment and remained seizure-free; 18/68 (26.5%) remained seizure-free after 24 weeks. 64/91 (70.3%) patients achieved ≥50% reduction in seizure frequency during maintenance treatment. This was accompanied by a mean 7.1 ± 16.00 point improvement from Baseline in the Quality of Life Inventory in Epilepsy (QOLIE-31-P) total score for 24-week completers, with improvement reported in all subscales. Most common treatment-emergent adverse events (TEAEs) were dizziness (31.3%) and headache (13.5%). In the later add-on cohort, 39/261 (14.9%) and 29/249 (11.6%) patients remained seizure-free after completing 12 and 24 weeks' treatment, respectively. 178/353 (50.4%) patients achieved ≥50% reduction in seizure frequency during maintenance treatment. Mean change in QOLIE-31-P total score was 4.8 ± 14.74 points among 24-week completers. Common TEAEs were dizziness (33.6%), somnolence (15.0%) and headache (11.4%).
Conclusions: Lacosamide initiated as first add-on treatment was efficacious and well tolerated in patients with uncontrolled POS.

1. Introduction

More than 30% of patients with epilepsy have been reported to be unable to achieve remission despite appropriate antiepileptic drug (AED) therapy [1].

Lacosamide is a newer AED, approved at dosages up to 400 mg/day as monotherapy or adjunctive therapy in adults (≥17 years)

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with partial-onset seizures (POS) in the USA [2], and as adjunctive therapy in adults (≥16 years) with POS in the EU [3] and other countries. The efficacy and safety of adjunctive lacosamide have been demonstrated in three randomised placebo-controlled trials that recruited patients with uncontrolled POS [4–6]. Most patients (84.4%) were taking multiple (two or three) concomitant AEDs, with a lifetime use (started but previously discontinued) of >4 AEDs by 77.4% patients, and >7 AEDs by 45.2% patients [7].

Since the chance of seizure freedom declines significantly with subsequent AED regimens [8], it is of interest to assess the response to adjunctive lacosamide when used earlier in treatment than in the pivotal studies, such as first add-on therapy. In this study, we sought to evaluate the efficacy and safety of lacosamide in two populations of adults with POS using an evaluation schedule similar to the registration trials. The 'first add-on' cohort of patients received lacosamide as their first adjunctive treatment after a first monotherapy, while the 'later add-on' cohort had previously been treated with at least two prior AED treatment regimens before adding lacosamide.

2. Methods

This was a prospective open-label, non-randomised, Phase IIIb/IV study (SP0954; NCT00955357), conducted between August 2009 and August 2013 at sites in Austria, Bulgaria, Czech Republic, Denmark, Finland, France, Greece, Italy, Romania, Russia, Spain, Turkey, Mexico and the USA, according to ICH-GCP [9], the Declaration of Helsinki, and local laws of the countries involved. All patients provided written informed consent and the study was approved by an Ethics Committee or Institutional Review Board for each site.

2.1. Patients

2.1.1. Overall study population

The study enrolled male or female adults (aged ≥18 years in Mexico or Bulgaria, ≥17 years in the USA and ≥16 years in all other countries). Patient enrolment criteria required a diagnosis of epilepsy with simple partial seizures (SPS) and a motor component or complex partial seizures (CPS) with or without secondarily generalised seizures (sGS). The maximum permitted seizure frequency (motor and non-motor) during the 12 weeks prior to screening (Historical Baseline) was 40 POS per 28 days. Patients were required to be lacosamide-naïve and maintained on a stable AED regimen for at least 7 days prior to screening, with or without concurrent stable vagus nerve stimulation.

Patients were excluded if they had a seizure disorder characterised primarily by POS without motor signs, a history of primary generalised seizures or status epilepticus, uncountable seizures due to clustering or possible non-epileptic seizures/events. Patients were also excluded if they had any medical or psychiatric condition that might compromise their health, ability to participate in the trial or could interfere with lacosamide pharmacokinetics.

2.1.2. First add-on cohort

Patients included in the first add-on cohort were taking an appropriate first monotherapy, defined as a single AED taken for at least 28 days prior to screening, and had no history of AED polytherapy. Prior short-term intermittent rescue therapy was accepted. At screening, patients had ≤24 months since epilepsy diagnosis, and experienced ≥3 POS (SPS with motor signs, CPS or sGS) at any time during the 12-week Historical Baseline.

2.1.3. Later add-on cohort

The later add-on cohort included patients with more treatment-refractory epilepsy, who were taking 1–3 AEDs, had received ≥2 prior AED treatment regimens (concurrently or sequentially), and had been diagnosed with epilepsy at least 5 years before screening. They had a POS frequency (SPS with motor signs, CPS or sGS) of ≥1 per 28 days during the 12-week Historical Baseline.

2.2. Treatment

The study design is shown in Supplemental Figure 1. Eligible patients received open-label twice-daily oral treatment with lacosamide tablets. Scheduled clinic visits were at screening (1 week before treatment initiation), and at Weeks 0 (treatment initiation), 5, 6 (end of Titration Phase), 12, 18, 24 and 30 (End of Maintenance Phase), followed by a Taper/Safety Follow-Up Phase of up to 3 weeks.

During the 6-week Titration Phase, lacosamide was initiated at 100 mg/day (50 mg bid) and then increased by 100 mg/day/week for 4 weeks to a maximum of 400 mg/day (200 mg bid). Changes to concomitant AED treatment were not allowed until the end of Weeks 4 and 5, when existing doses could be adjusted (no new AED additions were permitted). A reduction in the lacosamide dosage to 300 mg/day was permitted (if required) at the end of Week 5.

One increase (to a maximum of 400 mg/day) or decrease (to a minimum of 300 mg/day) of the lacosamide dose was allowed at the end of Week 12 of the Maintenance Phase. No other change to the lacosamide dose was permitted thereafter. Changes to concomitant AEDs were not allowed at any time during the Maintenance Phase. Patients who completed the 24-week Maintenance Phase and chose not to continue receiving commercial lacosamide were gradually tapered off.

2.3. Patient analysis sets

The Safety Set (SS) included all patients who received at least one dose of lacosamide during the study. The full analysis set (FAS) included patients of the SS who had at least one post-Baseline seizure assessment. The Completer Set (CS) was defined as patients of the FAS who completed the first 12 weeks of the Maintenance Phase. Patients in the FAS who completed the 24-week Maintenance Phase were considered 24-week completers.

2.4. Outcome measures and statistical analysis

The primary efficacy outcome was the proportion of patients among the CS who achieved seizure freedom, i.e. reported no seizures, with no missing seizure data, during the first 12 weeks of the Maintenance Phase.

The proportion of patients who achieved seizure freedom throughout the 24-week Maintenance Phase was also analysed among 24-week completers. The percentage change in POS frequency per 28 days was evaluated from Baseline to the first 12 weeks of maintenance therapy among the CS, and at the end of the 24-week Maintenance Phase in the FAS, using the last observation carried forward (LOCF) method. Responder rates (proportions of patients with ≥50% or ≥75% decrease in POS frequency per 28 days from Baseline) were analysed after 12 weeks of maintenance therapy among the CS, and at the end of the 24-week Maintenance Phase in the FAS (LOCF).

Other efficacy measures analysed among the FAS population included the change in clinical status measured by the Clinical Global Impression of Change (CGIC) and the Patient's Global Impression of Change (PGIC) at the end of the Maintenance Phase/Early Discontinuation. The Quality of Life (QOL) Inventory in Epilepsy-31-P (QOLIE-31-P) was completed by all capable patients to assess the effects of treatment on activities of daily living and overall health-related QOL across seven domains. The QOLIE-31-P is an adaptation of the QOLIE-31, grouped into seven subscales and

a weighted total score with additional items of 'distress' and 'prioritisation' for each subscale [10]. Total and subscale scores range from 0 to 100, where higher scores indicate better QOL. Mean change in QOLIE-31-P score from Baseline to the end of the 24-week Maintenance Phase was analysed for 24-week completers and the FAS using LOCF. Descriptive statistics were Cohen's d-effect size and p-values from paired t-tests. The proportion of patients achieving clinically meaningful improvements in QOL was estimated using previously defined thresholds [11].

Safety was assessed for the SS based on treatment-emergent adverse events (TEAEs), patient withdrawals due to TEAEs, vital signs and laboratory evaluations.

Seizure freedom and safety data were also analysed for subgroups of patients with or without concomitant use of one or more of the following traditional sodium channel-blocking (SCB) AEDs: carbamazepine, lamotrigine, oxcarbazepine, phenytoin, rufinamide and eslicarbazepine.

A descriptive analysis was used for all variables. Enrolment of 656 patients was planned and progressed more quickly for the later add-on cohort than the first add-on cohort. When recruitment closed, the target patient number was not reached for the first add-on cohort. Direct comparison between the first add-on and later add-on cohorts was neither planned, nor conducted, in this study.

3. Results

Of 461 patients enrolled in the study, 456 received at least one dose of lacosamide (SS), and 444 patients completed at least one post-baseline seizure assessment (FAS) (Fig. 1). Five patients were excluded from all analysis sets due to significant conduct deficiencies at one site. History of epilepsy and lifetime/concomitant AED use reflected the enrolment criteria for each cohort (Table 1). Concomitant SCB AEDs were taken by more patients in the later add-on cohort (74.2%) than in the first add-on cohort (54.2%).

3.1. First add-on cohort

Of 96 treated patients (SS), 80 (83.3%) completed the Titration Phase, 72 (75.0%) completed the first 12 weeks of the Maintenance Phase (CS), and 68 (70.8%) completed the 24-week Maintenance Phase (24-week completers) (Fig. 1).

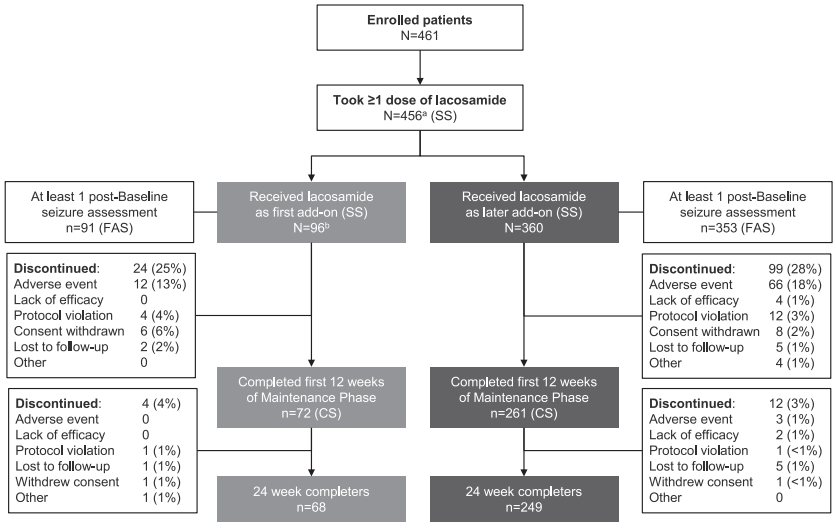
3.1.1. Efficacy

Seizure freedom was achieved by 37.5% of patients in the first add-on cohort who completed the first 12 weeks of the Maintenance Phase and by 26.5% of 24-week completers (Fig. 2A). POS frequency per 28 days decreased from Baseline to Week 12 of the Maintenance Phase (median percent change −91.3% [range −100% to 343.9%], CS) and during the 24-week Maintenance Phase (median change −90.5% [−100% to 1720%], FAS). This was associated with ≥50% responder rates of 76.4% after 12 weeks of maintenance therapy and 70.3% after 24 weeks (Fig. 2B). Among the subgroup of patients taking SCB AEDs and completing 12 weeks of maintenance therapy, 10/36 (27.8%) achieved seizure freedom, while 4/33 (12.1%) patients remained seizure-free after 24 weeks. Corresponding seizure freedom rates among patients taking non-SCB AEDs were 17/36 (47.2%) and 14/35 (40.0%).

At the end of treatment, clinicians rated patients' clinical status as improved for 73/86 (84.9%) patients in the first add-on cohort (FAS), comprising 20 patients (23.3%) considered very much improved, 41 (47.7%) much improved and 12 (14.0%) minimally improved (Supplemental Figure 2). Few patients were considered to have had no change (8/86, 9.3%) or worsened (5/86, 5.8%). A similar trend was seen for the patient-reported PGIC, with 66/83 (79.5%) patients indicating an improvement, comprising 21 (25.3%) very much improved, 36 (43.4%) much improved and 9 (10.8%) minimally improved; 9/83 patients (10.8%) had no change, and 8/83 (9.6%) worsened.

3.1.2. Quality of life

Among 24-week completers in the first add-on cohort there was an improvement in overall QOL with a mean ± SD change from Baseline in QOLIE-31-P total score of 7.1 ± 16.00 and an associated Cohen's *d*-effect size of 0.44 (Table 2), suggesting a moderate improvement. Using pre-defined thresholds [11], 49.2% (32/65) of completers showed a clinically meaningful improvement in the QOLIE-31-P total score (Supplemental Table 1). Improvements were observed across all subscale scores, with the greatest



[a]Five patients were excluded due to significant study conduct deficiencies at a single site
[b]Target number of patients for "first add-on" group was not reached when enrolment stopped
CS, Completer Set (eligible for primary efficacy endpoint analysis); FAS, full analysis set; SS, safety set

Fig. 1. Patient flow chart.

Table 1
Baseline characteristics (safety set).

	First add-on ($N=96$)	Later add-on ($N=360$)
Age, mean ± SD, years	41.0 ± 17.08	38.9 ± 12.34
Aged ≤18 years, *n* (%) patients	4 (4.2)	7 (1.9)
Aged ≥65 years, *n* (%) patients	10 (10.4)	4 (1.1)
Age range, min–max years	18–82	16–74
Female, *n* (%) patients	53 (55.2)	180 (50.0)
Body mass index, mean ± SD, kg/m^2	26.3 ± 5.75	26.5 ± 5.47
Racial group, *n* (%) patients		
White	79 (82.3)	278 (77.2)
Black	1 (1.0)	19 (5.3)
Asian	0	12 (3.3)
Other/mixed	16 (16.7)	51 (14.2)
Time since diagnosis, years		
Mean ± SD	1.1 ± 2.22	22.9 ± 13.11
Median (range)	0.7 (0.0–21.2)[a]	21.2 (3.6–65.5)
Seizure classification, *n* (%) patients		
I. POS[b]	96 (100.0)	360 (100.0)
Simple partial with motor signs	29 (30.2)	112 (31.1)
Complex partial	57 (59.4)	259 (71.9)
Partial evolving to sGS	69 (71.9)	241 (66.9)
II. Generalised seizures, *n* (%)	0	3 (0.8)
POS frequency/28 days, median (range)	2.8 (0.9–67.1)[c]	3.7 (0.3–36.6)
Any lifetime AED use,[d] *n* (%) patients	7 (7.3)[e]	338 (93.9)
0	89 (92.7)	22 (6.1)
1	6 (6.3)[e]	63 (17.5)
2	1 (1.0)[e]	107 (29.7)
3	0	50 (13.9)
≥4	0	118 (32.8)
Number of concomitant AEDs, *n* (%) patients		
0	1 (1.0)[f]	1 (0.3)[g]
1	95 (99.0)	100 (27.8)
2	0	170 (47.2)
3	0	87 (24.2)
4	0	2 (0.6)[h]
Most common concomitant AEDs at Baseline (≥10% of either cohort)		
Valproate	28 (29.2)	91 (25.3)
Carbamazepine	25 (26.0)	107 (29.7)
Oxcarbazepine	15 (15.6)	74 (20.6)
Levetiracetam	12 (12.5)	99 (27.5)
Lamotrigine	7 (7.3)	66 (18.3)
Phenytoin	5 (5.2)	42 (11.7)
Topiramate	1 (1.0)	46 (12.8)
Any concomitant SCB use, *n* (%) patients	52 (54.2)	267 (74.2)

AED, antiepileptic drug; POS, partial-onset seizure; SCB, sodium channel blocker; SD, standard deviation; sGS, secondarily generalised seizures.

[a] Two patients who had times since diagnosis of 21.2 and 6.3 years were initially placed in the later add-on cohort, and were later moved to the first add-on cohort because they were taking a first monotherapy.

[b] Patients may have experienced more than one type of seizure.

[c] One patient had a 28-day seizure frequency of >40 per month (motor and non-motor) in the 3 months prior to the Screening Visit.

[d] All AEDs taken by a patient and stopped at least 28 days prior to Screening.

[e] Seven patients in the first add-on cohort had at least one lifetime AED; these included valproate and phenytoin (two patients each), and clonazepam, diazepam, lamotrigine and carbamazepine (one patient each). One patient was listed as a protocol deviation; for the other six patients, the AED was not considered to be stable use.

[f] One patient was enrolled in the first add-on cohort despite not taking any AEDs at Baseline.

[g] One patient stopped taking lamotrigine on the date of the first dose of lacosamide, so not counted as a Baseline AED.

[h] Two patients had four concomitant AEDs at Baseline, but two of the concomitant AEDs were coded as different preferred terms despite being the same medication.

for seizure worry (+13.3 ± 26.44 points from Baseline). Across all subscales, 40.0–53.8% of patients showed clinically meaningful improvements. Similar results were noted for the FAS, with the exception of medication effects (−1.1 ± 33.23 points from Baseline); 39.8% of patients reported a clinically meaningful improvement.

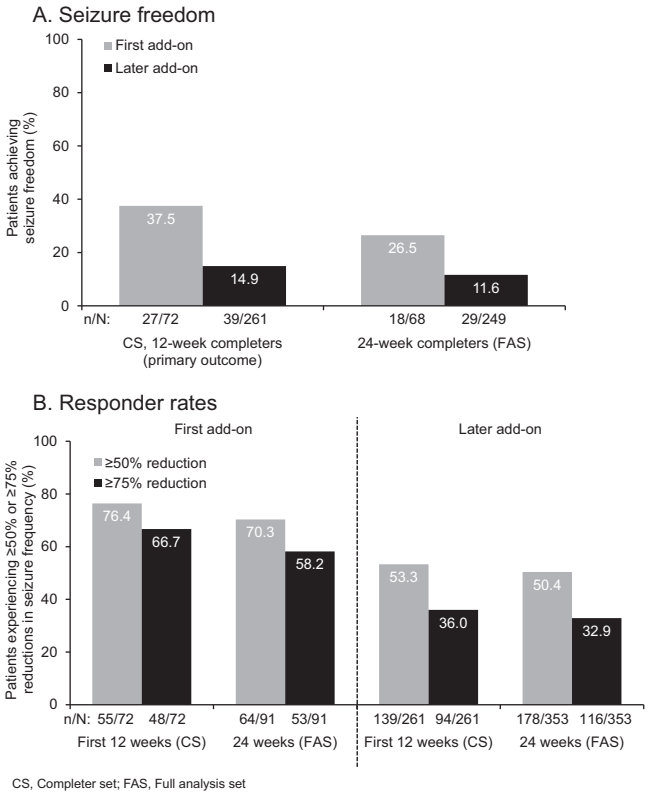


Fig. 2. Seizure control, seen as (A) seizure freedom, and (B) responder rates (proportions of patients achieving ≥50% or ≥75% reductions in seizure frequency from Baseline).

3.1.3. Safety and tolerability

During the Treatment Phase, the mean duration of lacosamide exposure in the first add-on cohort was 168.4 days, and the median mean exposure was 363.6 mg/day (Table 3).

TEAEs were reported for 69.8% of patients in the first add-on cohort, most frequently dizziness, headache, vertigo and nausea (Table 3). Most TEAEs were mild or moderate in intensity; 10 patients (10.4%) experienced a severe TEAE. The overall incidence of new-onset TEAEs was highest during the Titration Phase (Table 4).

TEAEs were reported by 71.2% of patients taking SCB AEDs (37/52) and 68.2% (30/44) of those taking non-SCB AEDs. The most commonly reported TEAEs among SCB AED users were dizziness (20/52, 38.5%), headache (7/52, 13.5%), vertigo (6/52, 11.5%), nausea, influenza (each 5/52, 9.6%), somnolence, anxiety and diplopia (each 4/52, 7.7%). The most commonly reported TEAEs among patients taking non-SCB AEDs were dizziness (10/44, 22.7%), headache (6/44, 13.6%), vertigo, nausea, diplopia, depression, irritability and nasopharyngitis (each 3/44, 6.8%).

TEAEs led to study discontinuation of 12 (12.5%) patients in the first add-on cohort (Table 3). The most common TEAE leading to discontinuation was dizziness, onset of which occurred during Titration for all patients. Eleven patients discontinued due to TEAEs with onset during the Titration Phase, 9 of who discontinued during the Titration Phase. Eight (8.3%) patients experienced serious adverse events (SAEs) and one patient died during the study; following a subdural haematoma caused by a fall, not considered by the investigator to be related to treatment.

No effect of lacosamide as a first add-on was observed for neurological and vital signs, laboratory results or ECG.

Table 2
Change from baseline in QOLIE-31-P scores and subscales for patients adding lacosamide as a first add-on or later add-on treatment (24-week Maintenance Phase completers).

	First add-on						Later add-on					
	Baseline		Change from Baseline		*P* value	Cohen's *d*-effect size	Baseline		Change from Baseline		*P* value	Cohen's *d*-effect size
	n	Mean ± SD	*n*	Mean ± SD			*n*	Mean ± SD	*n*	Mean ± SD		
Total score	68	60.5 ± 15.93	65	+7.1 ± 16.00	0.0007	0.44	245	59.7 ± 16.62	239	+4.8 ± 14.74	<0.0001	0.33
Seizure worry	68	44.4 ± 27.47	65	+13.3 ± 26.44	0.0001	0.50	248	43.9 ± 25.58	246	+6.9 ± 24.35	<0.0001	0.28
Overall QOL	68	60.0 ± 17.51	65	+8.5 ± 18.76	0.0005	0.46	248	61.4 ± 18.12	247	+6.0 ± 17.42	<0.0001	0.34
Emotional well-being	68	62.6 ± 19.69	65	+8.1 ± 22.00	0.0041	0.37	248	66.0 ± 19.94	246	+2.4 ± 18.90	0.45	0.13
Energy/fatigue	68	56.4 ± 18.78	65	+8.3 ± 20.85	0.0021	0.40	247	57.1 ± 19.51	242	+3.4 ± 19.27	0.0068	0.18
Cognitive	68	63.2 ± 24.46	65	+5.5 ± 21.68	0.045	0.25	248	61.8 ± 23.75	247	+3.0 ± 21.90	0.034	0.14
Medication effects	68	64.5 ± 25.66	65	+4.1 ± 28.96	0.26	0.14	247	59.9 ± 26.44	245	+2.9 ± 28.91	0.12	0.10
Social function	68	63.7 ± 21.87	65	+4.7 ± 27.09	0.16	0.17	247	59.0 ± 25.04	246	+8.1 ± 23.74	<0.0001	0.34

FAS, full analysis set; QOL, quality of life; SD, standard deviation. A positive change indicates an improvement. The *P* value is based on the paired *t*-test. Cohen's *d*-effect size is calculated by dividing the change from Baseline mean by the change from Baseline standard deviation.

3.2. Later add-on cohort

Of 360 treated patients (SS), 294 (81.7%) completed the Titration Phase, 261 (72.5%) completed the first 12 weeks of the Maintenance Phase (CS) and 249 (69.2%) completed the 24-week Maintenance Phase (24-week completers) (Fig. 1).

3.2.1. Efficacy

Seizure freedom was achieved by 39 of 261 (14.9%) patients in the later add-on cohort who completed the first 12 weeks of the Maintenance Phase, the majority of whom remained seizure-free (11.6%) for 24 weeks of maintenance therapy (Fig. 2A). POS frequency per 28 days decreased from Baseline to Week 12 of the Maintenance Phase (median percent change −54.8% [range −100% to 1668.7%], CS) and during the 24-week Maintenance Phase (median change −50.9% [−100% to 1720%], FAS). ≥50% responder rates were 53.3% after 12 weeks of maintenance therapy (CS) and 50.4% after 24 weeks (FAS; Fig. 2B). Among the subgroup of patients taking SCB AEDs and completing 12 weeks of maintenance therapy, 24/188 (12.8%) achieved seizure freedom, while 19/178 (10.7%) remained seizure-free after 24 weeks. Corresponding seizure freedom rates among patients taking non-SCB AEDs were 15/73 (20.5%) after 12 weeks and 10/71 (14.1%) after 24 weeks.

At the end of treatment, clinicians rated patients' clinical status as improved for 253/346 (73.1%) patients in the later add-on cohort (FAS), comprising 56 patients (16.2%) considered very much improved, 129 (37.3%) much improved and 68 (19.7%) minimally improved (Supplemental Figure 2). There was no change for 51/346 (14.7%) patients, and worse status for 42/346 (12.1%). Similarly, 231/326 (70.9%) patients indicated an improvement in PGIC (including 59 [18.1%] very much improved, 108 [33.1%] much improved and 64 [19.6%] minimally improved), while 47/326 patients (14.4%) rated no change and 48/326 patients [14.7%] worsened.

Table 3
Lacosamide exposure and safety profile (safety set) during the treatment phase.

Parameter	First add-on (*N* = 96)	Later add-on (*N* = 360)
Duration of lacosamide exposure, days	168.4 ± 73.6	165.2 ± 76.5
Mean ± SD	210.0 (7–222)	210.0 (1–260)
Median (min–max)		
Mean lacosamide exposure, median (min-max), mg/day	363.6 (100–381)	373.9 (61–400)
Any TEAE, *n* (%) patients	67 (69.8)	265 (73.6)
TEAEs occurring in ≥5% patients in either cohort		
Dizziness	30 (31.3)	121 (33.6)
Headache	13 (13.5)	41 (11.4)
Vertigo	9 (9.4)	22 (6.1)
Nausea	8 (8.3)	24 (6.7)
Diplopia	7 (7.3)	17 (4.7)
Somnolence	6 (6.3)	54 (15.0)
Anxiety	6 (6.3)	4 (1.1)
Influenza	5 (5.2)	4 (1.1)
Tremor	3 (3.1)	22 (6.1)
Vision blurred	2 (2.1)	24 (6.7)
Serious TEAEs, *n* (%)	8 (8.3)	17 (4.7)
Serious TEAEs reported by ≥2 patients		
Convulsion	2 (2.1)	1 (0.3)
Dizziness	0	2 (0.6)
Pyrexia	0	2 (0.6)
Serious TEAEs of interest, *n* (%)		
Agranulocytosis	0	1 (0.3)
Discontinuations due to TEAEs, *n* (%)	12 (12.5)	69 (19.2)
TEAEs leading to discontinuation of ≥2% patients of either cohort, *n* (%)		
Dizziness	4 (4.2)	33 (9.2)
Headache	2 (2.1)	9 (2.5)
Convulsion	2 (2.1)	3 (0.8)
Depression	2 (2.1)	0
Somnolence	0	9 (2.5)
Deaths, *n* (%)	1[a] (1.0)	0

TEAE, treatment-emergent adverse event with onset during the Treatment Phase (Titration or Maintenance), listed as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms; SD, standard deviation.
[a] Subdural haematoma, not considered to be related to study medication.

3.2.2. Quality of life

Among 24-week completers in the later add-on cohort there was an improvement in overall QOL with a mean ± SD change from Baseline in QOLIE-31-P total score of +4.8 ± 14.74 points and an associated Cohen's *d*-effect size of 0.33 (Table 2). Using pre-defined thresholds [11], 43.1% of completers (103/239) showed clinically meaningful improvements in the QOLIE-31-P total score (Supplemental Table 1). Improvements were observed across all subscales with the greatest improvement for social function (+8.1 ± 23.74 points from Baseline). Across all subscales, 36.0–53.7% of patients showed clinically meaningful improvements. Similar results were noted for the FAS, with the exception of medication effects (−2.4 ± 30.28 points from Baseline); 37.5% of patients reported a clinically meaningful improvement.

3.2.3. Safety and tolerability

Mean duration of lacosamide exposure during the Treatment Phase in the later add-on cohort was 165.2 days, and median mean exposure was 373.9 mg/day (Table 3).

TEAEs were reported for 73.6% of patients in the later add-on cohort, most frequently dizziness, somnolence and headache (Table 3). Most TEAEs were mild or moderate in intensity; 36

Table 4
Incidence of most common TEAEs[a] by study phase (safety set).

Incidence, *n* (%)	First add-on (*N* = 96)			Later add-on (*N* = 360)		
	Titration	Maintenance weeks 1–12	Maintenance weeks 12–24	Titration	Maintenance weeks 1–12	Maintenance weeks 12–24
Patients entering the study phase	96	80	72	360	294	261
Any TEAE with onset during study phase	58 (60.4)	25 (31.3)	16 (22.2)	236 (65.6)	89 (30.3)	59 (22.6)
Patients reporting the most common TEAEs,[a] with onset during respective study phase						
Dizziness	28 (29.2)	3 (3.8)	1 (1.4)	109 (30.3)	20 (6.8)	6 (2.3)
Headache	8 (8.3)	6 (7.5)	1 (1.4)	37 (10.3)	8 (2.7)	2 (0.8)
Vertigo	8 (8.3)	1 (1.3)	0	17 (4.7)	2 (0.7)	3 (1.1)
Nausea	6 (6.3)	0	2 (2.8)	22 (6.1)	2 (0.7)	0
Diplopia	6 (6.3)	0	1 (1.4)	17 (4.7)	1 (0.3)	0
Somnolence	5 (5.2)	2 (2.5)	0	51 (14.2)	4 (1.4)	3 (1.1)
Anxiety	4 (4.2)	1 (1.3)	1 (1.4)	4 (1.1)	0	0
Influenza	3 (3.1)	1 (1.3)	1 (1.4)	2 (0.6)	0	2 (0.8)
Tremor	2 (2.1)	0	1 (1.4)	21 (5.8)	2 (0.7)	0
Vision blurred	2 (2.1)	0	0	21 (5.8)	2 (0.7)	1 (0.4)

TEAE, treatment-emergent adverse event.
[a] TEAEs with overall incidence of over 5% in either cohort during the Treatment Phase (Titration plus Maintenance Phase).

patients (10.0%) experienced a severe TEAE. The overall incidence of new-onset TEAEs was highest in the Titration Phase (Table 4).

TEAEs were reported by 76.4% of patients taking SCB AEDs (204/267) and 65.6% (61/93) of those taking non-SCB AEDs. The most commonly reported TEAEs among SCB AED users were dizziness (103/267, 38.6%), somnolence (36/267, 13.5%), headache (33/267, 12.4%), vision blurred (21/267, 7.9%), vertigo (20/267, 7.5%), nausea (18/267, 6.7%) and diplopia (16/267, 6.0%). The most commonly reported TEAEs among users of non-SCB AEDs were dizziness, somnolence (each 18/93, 19.4%), tremor (9/93, 9.7%), headache (8/93, 8.6%), nausea, irritability and urinary tract infection (each 6/93, 6.5%).

TEAEs led to study discontinuation of 69 (19.2%) patients in the later add-on cohort (Table 3): 46 (12.8%) patients discontinued due to TEAEs during the Titration Phase, 20 (5.6%) discontinued during the first 12 weeks of the Maintenance Phase and three (0.8%) during the last 12 weeks of the Maintenance Phase. The most common TEAE leading to discontinuation was dizziness, which had an onset during Titration for 29/33 patients.

Seventeen (4.7%) patients in the later add-on cohort experienced SAEs (Table 3). The incidence of TEAEs involving haematology and clinical chemistry values was low, including one serious TEAE of agranulocytosis, and two clinical chemistry-related SAEs (hypochloraemia and hyponatraemia, both not considered treatment-related and occurred in the same patient). The event of agranulocytosis occurred in a 25-year-old male patient who had been on study medication for 46 days and was taking 400 mg/day lacosamide adjunctive to lamotrigine and levetiracetam at the time of the event. The SAE was classified as related to lacosamide treatment, which was discontinued. The TEAE resolved in 7 days. There was one clinically significant ECG abnormality (a SAE of ST elevation, considered possibly related to study medication and leading to discontinuation of 100 mg/day lacosamide, taken adjunctive to carbamazepine and levetiracetam). No consistent or clinically relevant effect of lacosamide as a later add-on was observed for neurological and vital signs, or laboratory results.

4. Discussion

Lacosamide has been extensively evaluated in difficult-to-treat patients. The results of this study indicated that lacosamide is also efficacious as a first add-on treatment for uncontrolled POS.

The antiepileptic efficacy achieved with first add-on lacosamide supports previous studies of early lacosamide use, with 26.5% of patients remaining seizure-free over 24 weeks of maintenance therapy and 70% responding with ≥50% reductions in seizure frequency. Although a potential limitation of this study is the 6-month duration for evaluation of seizure freedom (in accordance with the ILAE consensus definition, 12 months is typically required among patients with treatment-refractory epilepsy [12]), similar findings were observed in the non-interventional VITOBA study, where lacosamide initiated as an add-on to monotherapy for POS led to seizure freedom during the final 3 months of the 6-month study in 45.5% of 494 patients taking in-label doses, and 72.5% of patients showed a ≥50% response [13]. In that study, of the 190 patients who received lacosamide after first monotherapy, 60.5% became seizure-free and 82.1% showed ≥50% response. Somewhat lower seizure freedom and ≥50% response rates were seen among the 304 patients who had received more than one previous AED [13]. Despite differences in the definition of seizure freedom, the retrospective, observational LACO-EXP study also reported that the proportion of ≥50% responders during lacosamide therapy progressively declined with increasing numbers of prior AEDs [14]. Prospective audits of lacosamide and other newer agents support these findings, showing seizure freedom was more commonly achieved in patients treated for uncontrolled POS when added as a first or second add-on [15].

Interpretation of the findings from this study is limited by the open-label, non-randomised design, and the failure to enrol the target number of patients in the first add-on cohort. This resulted in an imbalance in patient numbers between the two cohorts. Direct comparison between first-add-on and later add-on cohort was neither planned nor possible.

In the current study, 11.6% of patients who added lacosamide later in their therapy achieved seizure freedom for 24 weeks after initiating lacosamide treatment. This was somewhat higher than the 3.3% of patients in registration trials who took 400 mg/day lacosamide adjunctive to 1–3 AEDs (83.3% 2–3 AEDs) for 16–18 weeks [4–6]. A ≥50% reduction in seizure frequency was reported by 50.4% of patients in the current study, also higher than that observed for patients who took 400 mg/day lacosamide in the registration trials (39.7%) [7]. Although the duration of epilepsy was comparable for patients in this study and those in the registration trials, later add-on patients in the current study reported fewer lifetime AEDs (32.8% vs. 77.4% had used at least 4 AEDs) and had a lower median Baseline seizure frequency (3.7 vs. 11.5/28 days). Nonetheless, it should be noted that use of a retrospective Baseline in this study may have underestimated the Baseline seizure frequency compared with the prospective Baselines used in the registration trials. Responder and seizure freedom rates comparable to those observed here have previously been

reported with lacosamide therapy in treatment-refractory patients. In the LACO-EXP study, 14.9% of patients taking lacosamide at a median dosage of 400 mg/day were seizure-free for the 12-month study, with 57.1% considered to be ≥50% responders [14]. Poorer efficacy outcomes are generally expected from more refractory epilepsy populations [8,14,16,17], however, findings from this study support a conclusion that improvements in seizure frequency may be obtained with lacosamide treatment taken as a first or later add-on therapy.

The antiepileptic efficacy of lacosamide was accompanied by improvements in QOL and in patient- and physician-rated overall clinical health status. In this study, mean changes in QOLIE-31-P from Baseline and Cohen's d-effect sizes showed improvements in overall QOL both in study completers and the FAS, being numerically higher in the first add-on group. Across all QOLIE-31-P subscales, clinically relevant improvements were observed in 40.0–53.8% of 24-week completers in the first add-on cohort, when assessed using pre-defined thresholds [11]. An improvement in medication effects was seen in 43.1% of completers, which, alongside the 12.5% of patients discontinuing the study due to AEs, supports the conclusion that 300–400 mg/day lacosamide was well tolerated in this patient cohort. The greatest improvement was observed for seizure worry, most likely reflecting the reduced seizure frequency achieved in these patients. Among 24-week completers in the later add-on cohort, clinically relevant improvements were observed for in 36.0–53.7% of patients across all QOLIE-31-P subscales. In the later add-on FAS population, QOLIE-31-P scores were consistent with QOL improvements seen among refractory patients in a Phase IIb trial (at 400 mg/day lacosamide, assessed using the QOLIE-31 scale [4] and among responders to lacosamide therapy in a pooled analysis [18]. These findings suggest a positive effect on QOL with adjunctive lacosamide therapy added early or later into the treatment paradigm.

Post hoc analyses of controlled studies in adults with focal epilepsy have shown the pharmacokinetic profile of lacosamide to be unaffected by age (16–71 years) or gender [19], with pharmacokinetic studies currently underway in paediatric patients (including SP0847 [NCT00938431], SP0969 [NCT01921205] and SP1047). However, evaluation of the safety and effectiveness of lacosamide therapy among patient sub-groups in a setting which more closely represents real-life clinical practice is of additional interest, in particular, findings among patients adding lacosamide to traditional SCB AEDs and in those taking AEDs with a different mode of action. Some studies have reported similar seizure control among these patient subgroups [13,20]. However, exploratory analyses undertaken in the current study are consistent with other reports [14,17,21,22] indicating that seizure freedom was more achievable in patients adding lacosamide to treatment regimens which do not include traditional SCB AEDs. This was particularly true in patients who added lacosamide to a first AED. Although lacosamide is not a traditional SCB AED, these findings may be attributed to the ability of lacosamide to selectively facilitate slow inactivation of sodium channels [23]. However, due to the uncontrolled nature of this study and the small numbers of patients in each subgroup, caution should be applied when interpreting such observations.

Alongside positive efficacy findings and observed in improvements quality of life, the safety profile for lacosamide 300–400 mg/day when initiated as a first or later add-on therapy was consistent with the known profile for adjunctive lacosamide [4–6], with tolerability improving over the study duration. Pharmacokinetic assessments have shown lacosamide to have limited interactions with a range of other AEDs, and consistent with previous studies, the nature of the most commonly reported TEAEs were similar in patients adding lacosamide to a regimen with or without a SCB AED [2,7,21].

5. Conclusion

The results of this study support the use of lacosamide as an efficacious and well-tolerated agent for the early treatment of uncontrolled POS. They highlight the potential for a substantial number of patients to achieve seizure freedom and marked reductions in seizure frequency when treated with lacosamide as a first add-on therapy at doses of 300–400 mg/day.

Conflicts of interest

Wendy Waldman Zadeh has served on Speakers' Bureaus for Allergan and Cyberonics. Antonio Escartin has received compensation from Serono, Bayer and Novartis for speaking and serving on a scientific advisory board. William Byrnes, Frank Tennigkeit, Peter Dedeken, Marc De Backer, Simon Borghs and Ting Li are employees of UCB Pharma.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.07.001.

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