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Safety and tolerability of adjunctive lacosamide in a pediatric population with focal seizures – An open-label trial

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ABSTRACT

Purpose: To evaluate safety and tolerability of adjunctive lacosamide in children with focal seizures.
Methods: Patients were eligible for this open-label, fixed-titration trial (SP0847; NCT00938431) if aged 1 month–17 years with focal seizures taking 1–3 antiepileptic drugs. Findings from Cohort 1, aged 5–11 years, who received lacosamide ≤8 mg/kg/day, informed dosing for age-based cohorts 2–5, who then received ≤12 mg/kg/day (≤600 mg/day). Oral lacosamide was initiated at 2 mg/kg/day (1 mg/kg bid) and uptitrated by 2 mg/kg/day/week to the maximum cohort-defined dose (maximum trial duration: 13 weeks). Patients who did not achieve the maximum cohort-defined dose were discontinued.
Results: Forty-seven patients (aged 6 months–≤17 years) enrolled (≥1 month– < 4 years: $n = 15$; ≥4– < 12 years: $n = 23$; ≥12–≤17 years: $n = 9$). 24/47 (51.1%) patients completed the trial at the maximum cohort-defined dose and 40/47 (85.1%) continued lacosamide in the extension trial. Treatment-emergent adverse events (TEAEs) were reported by 42/47 (89.4%) patients. The most common TEAEs (≥10% of patients) were vomiting (21.3%), diarrhea (14.9%), somnolence (12.8%), irritability, dizziness, and pyrexia (10.6% each). Twenty (42.6%) patients discontinued due to TEAEs, most commonly vomiting (8.5%), gait disturbance, dizziness, and somnolence (6.4% each). Six (12.8%) patients reported serious TEAEs, most commonly status epilepticus (3/47; 6.4%).
Conclusion: This fixed-titration trial supports the safety of adjunctive lacosamide in children (aged 6 months–≤17 years) with focal seizures. The TEAE profile was generally consistent with that observed in trials in adults, and no new safety concerns were identified.

1. Introduction

Focal (partial onset) seizures are often treated similarly in children over 4 years of age and in adolescent or adult patients [1,2]. As in adults, over 25% of children have inadequate seizure control on currently available antiepileptic drugs (AEDs), or have experienced significant adverse drug effects [3,4]. In general, there are fewer data from randomized controlled trials to guide the treatment of epilepsy in pediatric patients compared with adults [5].

Lacosamide has a mechanism of action which differs from most other sodium channel-blocking (SCB) AEDs; it selectively enhances the slow inactivation of neuronal voltage-gated sodium channels without affecting fast inactivation [6,7]. Lacosamide is indicated for the treatment of focal seizures in patients 4 years of age and older in the European Union and the United States (US) [8,9]. Approval of lacosamide for use in adults was based on data from three double-blind,

Abbreviations: AED, antiepileptic drug; bid, twice daily; CaGI-C, Caregiver's Global Impression of Change; CGI-C, Clinical Global Impression of Change; ECG, electrocardiogram; FAS, Full Analysis Set; MedDRA, Medical Dictionary for Regulatory Activities; PK, pharmacokinetic; RSE, Relative Standard Error; SCB, sodium channel-blocking; SD, standard deviation; SS, Safety Set; TEAE, treatment-emergent adverse event

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randomized, placebo-controlled, phase III trials [10–12]. Pediatric approval of lacosamide was based on extrapolation of efficacy data from adolescents and adults, and safety and pharmacokinetic (PK) data from open-label trials of adjunctive lacosamide therapy in children [8]. The availability of lacosamide as oral tablet, oral solution, and intravenous solution provides added therapeutic flexibility, with the oral solution potentially being useful for children who may find it difficult to swallow tablets.

Several retrospective or prospective, open-label studies have evaluated the use of lacosamide in pediatric patients with epilepsy [13–24]. Findings from the prospective, open-label, fixed-titration trial reported here were used to guide lacosamide dosing in subsequent phase II/III trials further assessing safety and efficacy of adjunctive lacosamide. These included the double-blind, placebo-controlled phase III trial that demonstrated efficacy of adjunctive lacosamide in children and adolescents aged ≥4 to < 17 years with uncontrolled focal seizures [25,26].

This article reports the findings from a phase II, multinational, open-label, fixed-titration trial, specifically designed to assess the safety, tolerability, and PK of lacosamide oral solution added to one to three concomitant AEDs for the treatment of focal seizures in children aged 1 month to 17 years. PK data are reported separately [27].

2. Methods

2.1. Trial design

This phase II, multinational, open-label, fixed-titration trial was conducted in Belgium, Mexico, and the US (SP0847, NCT00938431). Trial protocol and parent/patient informed consents/assents were reviewed by regional, national, independent, or institutional ethics committees, as appropriate, and met the requirements of the Declaration of Helsinki and all local laws. The trial was conducted in accordance with the applicable International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent from patients' parents/legal guardians or assent from patients, where appropriate, was obtained.

Initial dosing of lacosamide oral solution (10 mg/mL) was based on the doses used in previous adult trials, adjusted to mg/kg. The minimum recommended adult dose (200 mg/day) was divided by the minimum weight of an adult (50 kg), to produce a minimum target dose of 4 mg/kg/day, split equally across two daily doses.

Results of PK and tolerability assessments from Cohort 1 (aged 5 to 11 years; ≥6 patients, target maximum dose 8 mg/kg/day) were used to determine if lacosamide dosing was safe and resulted in plasma concentrations within the range observed in adults receiving therapeutic lacosamide doses. The results from Cohort 1 informed the number of patients and maximum dosage for use in Cohorts 2–5. Based on results from Cohort 1, up to four additional age-stratified cohorts were to be enrolled with a maximum dose of 12 mg/kg/day (Cohort 2: ≥10 patients aged 12 to 17 years; Cohort 3: ≥10 patients aged 2 to 4 years; Cohort 4: ≥6 patients aged 5 to 11 years; Cohort 5: ≥12 patients aged 1 month to 2 years).

The trial consisted of a Screening Period (up to 2 weeks), Treatment Period (up to 6 weeks of titration followed by 3 days at maximum recommended/tolerated dose), and a 2-week End-of-Study Period (taper or transition), with a maximum trial duration of 13 weeks. Patients that met the eligibility criteria entered the Treatment Period and received lacosamide oral solution (10 mg/mL) at a starting dose of 2 mg/kg/day (1 mg/kg/day, twice daily). A fixed-titration schedule was used to increase the dose by 2 mg/kg/day per week towards the maximum cohort-defined target dose (8 mg/kg/day for Cohort 1, 12 mg/kg/day [not exceeding 600 mg/day] for Cohorts 2–5). Patients must have been on each dose for at least 5 days before uptitration to the next dose. Patients reaching a maximum tolerated dose that was below the cohort-defined maximum were discontinued.

Serial blood sampling for the determination of lacosamide plasma concentrations was performed during the titration to 4 mg/kg/day, and at the end of Treatment Period with the maximum recommended or tolerated lacosamide dose. To ensure steady state concentrations, blood samples were collected after at least 3 days on the respective dose. One 2 mg/kg/day dose reduction was allowed if the patient had achieved a dose of at least 4 mg/kg/day. Once back-titration occurred, the dose could not be increased and the patient had to remain on the reduced dose for at least 3 days for PK sampling.

Patients could enter the open-label extension trial (SP848, NCT00938912), if they had completed SP0847 at the maximum-defined cohort dose, or had discontinued because of a dose reduction or status epilepticus. Those who chose not to continue in the extension trial had their lacosamide dose tapered with a safety follow-up performed 28–35 days after receiving their final lacosamide treatment.

2.2. Patients

Eligible patients were aged ≥1 month to ≤17 years with a confirmed diagnosis of epilepsy with focal seizures, which were uncontrolled despite treatment with two or more concurrent or sequential AEDs. For patients aged < 1 year, the corrected gestational age was used. Patients must have experienced two or more countable seizures in the 4 weeks before screening, and must have been on a stable dose of one to three AEDs for at least 1 week before screening and throughout the trial. Use of a vagus nerve stimulator was permitted and not counted as an AED. Key exclusion criteria were uncountable seizures (i.e., because of clustering), which would preclude the explorative evaluation of therapeutic benefit, a history of primary generalized seizures, or status epilepticus within 6 months (patients ≥2 years of age) or 1 month (patients < 2 years of age) of screening. Furthermore, patients with a clinically relevant electrocardiogram (ECG) abnormality, hemodynamically significant heart disease, arrhythmic heart condition requiring medical therapy, or known sodium channelopathy were excluded.

2.3. Outcomes

Primary safety outcomes were the incidence of treatment-emergent adverse events (TEAEs), withdrawals due to TEAEs, changes in hematology, clinical chemistry, urinalysis and endocrinology values, 12-lead ECG recordings, vital signs, and physical or neurological examinations. Serious TEAEs were defined as those that required hospitalization, were life-threatening, led to death, disability, or congenital defects. The assessment of seriousness was made independently of the TEAE intensity (mild, moderate, or severe [considered unable to conduct routine activities]).

At each visit during the Treatment Period, two interpretable ECG recordings were performed approximately 20–30 min apart before lacosamide dosing. Two further interpretable recordings were collected 30 min to 1 h after titration to doses ≥8 mg/kg/day lacosamide, and at the final visit, when patients were at steady state on their maximum tolerated/maximum cohort-defined lacosamide dose. Baseline ECG values were defined as the average of any pre-treatment ECG recordings.

Efficacy outcomes were exploratory, with seizure frequency data collected using seizure diaries and a Historical Baseline consisting of the 4 weeks before screening. Outcomes included: median percent change in seizure frequency/28 days from Baseline to Treatment; the proportion of patients with a ≥25% increase, no change (between < 25% reduction and < 25% increase), a ≥50% reduction, or a ≥75% reduction in seizure frequency, from Baseline to Treatment; and the Clinical Global Impression of Change (CGI-C) and Caregiver's Global Impression of Change (CaGI-C) at the end of treatment.

Post hoc subgroup analyses of safety and efficacy outcomes were performed for patients taking at least one concomitant SCB AED

(carbamazepine, lamotrigine, oxcarbazepine, or phenytoin derivatives) at Baseline and patients not on concomitant SCB AEDs.

PK data from this trial were used to develop a population PK model, and the results are published separately [27].

2.4. Statistical analyses

Sample size was determined using the optimal design software PFIMOPT version 3.0 [28]. The optimization results indicate that 24 patients and six PK samples per patient (i.e., three samples for each of the planned two visits with PK sampling) are appropriate for determining the structural PK parameters of lacosamide with good precision (about 3% mean Relative Standard Error [RSE] on clearance, 7% RSE on distribution volume, and 25% RSE for rate constant of absorption). The sample size was first increased to 30, as the actual precision may have been lower, and then to 42 by the addition of the cohort of patients aged ≥1 month to < 2 years. Data were pooled and summarized by age groups defined by age at enrollment (≥1 month to < 4 years, ≥4 to ≤12 years, and ≥12 to ≤17 years). All analyses were descriptive in nature.

Safety outcomes were reported for the Safety Set (SS), which included all patients who received at least one dose of lacosamide. Exploratory efficacy outcomes were reported for the Full Analysis Set (FAS), which included all patients from the SS who had one or more post-Baseline seizure diary entries.

3. Results

3.1. Patient disposition

Forty-seven patients entered the trial and received lacosamide, forming the SS (Fig. 1). Of these patients, 23 (48.9%) discontinued the trial. Twenty patients discontinued due to adverse events (42.6%). Forty patients (85.1%) continued lacosamide in the extension trial. Forty-six patients took one or more doses of lacosamide and had at least one post-Baseline seizure diary entry, forming the FAS.

Cohort 1 (5–11 years of age, $n = 7$) achieved a maximum daily lacosamide dosage of up to 8 mg/kg/day; consequently, four subsequent cohorts were recruited and had a maximum daily dosage of up to 12 mg/kg/day (Cohort 2: 12–17 years [$n = 9$], Cohort 3: 2–4 years [$n = 8$], Cohort 4: 5–11 years [$n = 11$], and Cohort 5: 1 month to < 2 years [$n = 12$]).

3.2. Patient demographics and epilepsy characteristics

Patient demographics and epilepsy characteristics were summarized by age groups (Table 1; SS). The overall patient age range was 6 months to 17 years.

Patients aged < 4 years had a higher focal seizure frequency during the 4-week Historical Baseline than those aged 4–17 years (median 23.0 [range: 3.0–384.0] per 28 days vs. 10.5 [2.0–122.0] per 28 days, respectively). Levetiracetam was the most frequently used concomitant AED (44.7%), followed by lamotrigine (36.2%) and oxcarbazepine (25.5%). While levetiracetam use was similar in patients across all age groups, lamotrigine and oxcarbazepine use was higher in older (≥4 years) than younger patients.

3.3. Lacosamide exposure

Mean daily dose during the Treatment Period was 5.82 mg/kg/day (standard deviation 1.37). Maximum lacosamide dose was 4 mg/kg/day for 2.1% (1/47), 6 mg/kg/day for 8.5% (4/47), 8 mg/kg/day for 29.8% (14/47), 10 mg/kg/day for 14.9% (7/47), and 12 mg/kg/day for 44.7% (21/47) (Table 2; SS). Overall, 51.1% (24/47) of patients completed the

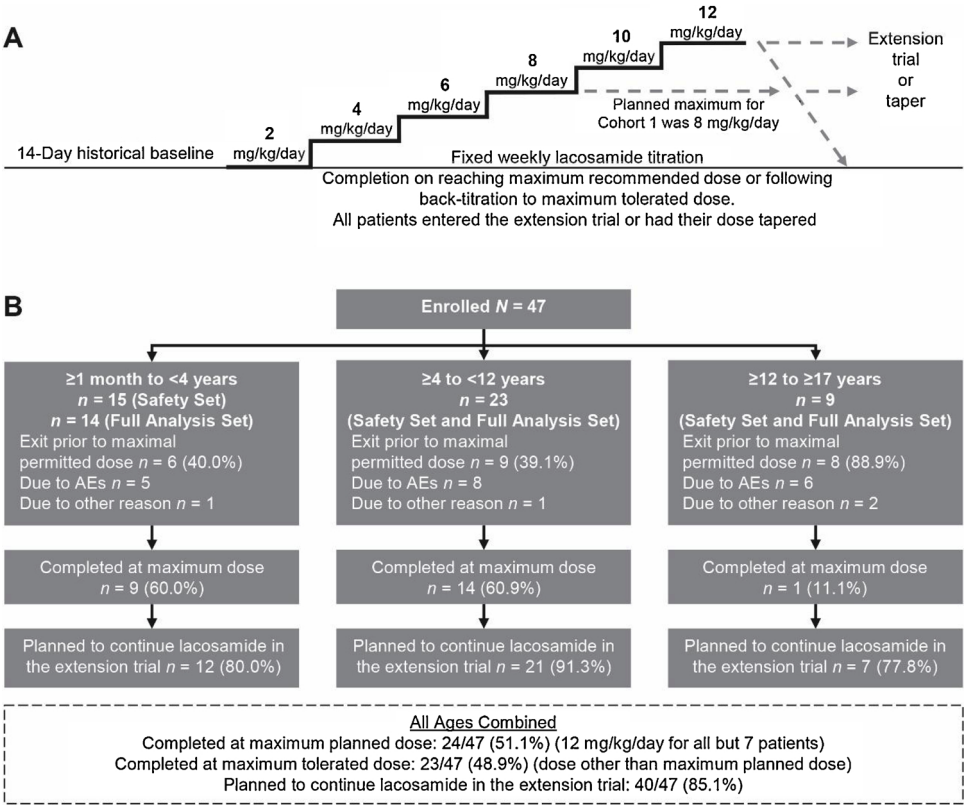

Fig. 1. Trial design (A) and patient disposition (B). Lacosamide dosage was not to exceed 12 mg/kg/day or 600 mg/day. Data were later summarized in the three main age groups shown.

Table 1
Patient demographics and epilepsy characteristics (SS).

	≥1 month to < 4 years (*n* = 15)	≥4 to ≤17 years			All patients ≥1 month to ≤17 years (*n* = 47)
		≥4 to < 12 years (*n* = 23)	≥12 to ≤17 years (*n* = 9)	Combined ≥4 to ≤17 years (*n* = 32)	
Age, mean (SD), years	1.6 (1.0)	7.4 (2.4)	15.2 (1.5)	9.6 (4.2)	7.0 (5.1)
Female, *n* (%)	10 (66.7)	9 (39.1)	5 (55.6)	14 (43.8)	24 (51.1)
Race, *n* (%)					
White	7 (46.7)	18 (78.3)	5 (55.6)	23 (71.9)	30 (63.8)
Black	0	4 (17.4)	3 (33.3)	7 (21.9)	7 (14.9)
Asian	1 (6.7)	1 (4.3)	0	1 (3.1)	2 (4.3)
Other/mixed	7 (46.7)	0	1 (11.1)	1 (3.1)	8 (17.0)
Time since epilepsy diagnosis, mean (SD), years	0.8 (0.5)	5.3 (2.8)	7.6 (4.4)	5.9 (3.4)	4.3 (3.7)
Age at epilepsy diagnosis, mean (SD), years	0.8 (1.0)	2.2 (2.3)	7.6 (5.2)	3.7 (4.1)	2.8 (3.7)
Seizure classification history[a,b], *n* (%)					
Any partial-onset (focal) seizures	15 (100)	23 (100)	9 (100)	32 (100)	47 (100)
Partial evolving to secondarily generalized (focal to bilateral tonic-clonic)	8 (53.3)	13 (56.5)	7 (77.8)	20 (62.5)	28 (59.6)
Focal seizure frequency per 28 days, median (range)	23.0 (3–384)	11.0 (2–100)	5.0 (3–122)	10.5 (2–122)	11.0 (2–384)
Lifetime AEDs[c], *n* (%)					
1–3	7 (46.7)	10 (43.5)	5 (55.6)	15 (46.9)	22 (46.8)
4–6	4 (26.7)	7 (30.4)	1 (11.1)	8 (25.0)	12 (25.5)
≥7	0	4 (17.4)	2 (22.2)	6 (18.8)	6 (12.8)
Missing	4 (26.7)	2 (8.7)	1 (11.1)	3 (9.4)	7 (14.9)
Concomitant AEDs, *n* (%)					
1	4 (26.7)	4 (17.4)	2 (22.2)	6 (18.8)	10 (21.3)
2	9 (60.0)	14 (60.9)	6 (66.7)	20 (62.5)	29 (61.7)
3	2 (13.3)	5 (21.7)	1 (11.1)	6 (18.8)	8 (17.0)
Use of concomitant SCB AEDs[d], *n* (%)	5 (33.3)	17 (73.9)	8 (88.9)	25 (78.1)	30 (63.8)
Concomitant AEDs[e,f], *n* (%)					
Levetiracetam	7 (46.7)	10 (43.5)	4 (44.4)	14 (43.8)	21 (44.7)
Lamotrigine	1 (6.7)	11 (47.8)	5 (55.6)	16 (50.0)	17 (36.2)
Oxcarbazepine	1 (6.7)	5 (21.7)	6 (66.7)	11 (34.4)	12 (25.5)
Valproate	6 (40.0)	4 (17.4)	1 (11.1)	5 (15.6)	11 (23.4)
Topiramate	3 (20.0)	4 (17.4)	0	4 (12.5)	7 (14.9)
Phenobarbital	3 (20.0)	0	0	0	3 (6.4)
Use of vagal nerve stimulation, *n* (%)	0	3 (13.0)	2 (22.2)	5 (15.6)	5 (10.6)

AED, antiepileptic drug; SCB, sodium channel-blocking; SD, standard deviation; SS, Safety Set.
Data are *n* (%) patients or mean (SD).
[a] Patients could have experienced more than one type of seizure. Focal seizures include those with or without impairment of awareness, or observable motor signs.
[b] Seizure types are listed per the trial protocol (ILAE 1981 [29]), with the ILAE 2017 classification [30] provided in parentheses.
[c] Any AED previously taken but discontinued before first lacosamide dose.
[d] Concomitant traditional sodium channel-blocking AEDs: carbamazepine, lamotrigine, oxcarbazepine, and phenytoin derivatives.
[e] Only those AEDs taken by ≥20% of patients in any age group are listed.
[f] Patients could be taking more than one concomitant AED.

Table 2
Maximum lacosamide dose by age group (SS).

Age group	Enrolled patients, *n*	Maximum lacosamide dose (mg/kg/day)				
		4	6	8	10	12
≥1 month to < 4 years	15	0	2	2	1	10
≥4 to < 12 years	23	0	1	9[a]	3	10
≥12 to ≤17 years	9	1	1	3	3	1
Total ≥4 to ≤17 years	32	1	2	12[a]	6	11
All patients	47	1	4	14[a]	7	21

SS, Safety Set.
[a] Cohort 1 contained seven patients of ≥5 to ≤11 years of age who could titrate up to a maximum recommended dose of 8 mg/kg/day, or until maximum tolerated dose was achieved. All other patients could titrate up to a maximum recommended dose of 12 mg/kg/day, or 600 mg/day, whichever came sooner.

final planned visit at the maximum cohort-defined recommended dose and 48.9% (23/47) discontinued at their maximum tolerated dose. The mean treatment duration for all patients was 40.4 days, and was similar across age groups.

3.4. Primary safety outcomes

TEAEs were reported by 89.4% (42/47) of patients and by a similar proportion in each age group; 93.3% (14/15) aged < 4 years, 82.6% (19/23) aged 4–12 years, and 100% (9/9) aged 12–17 years (Table 3; SS). Overall, the most commonly reported TEAEs were vomiting (10/47 [21.3%]), diarrhea (7/47 [14.9%]), and somnolence (6/47 [12.8%]). Twenty-eight patients (59.6%) experienced a TEAE that was considered by the investigator to be lacosamide-related, but the overall incidence of each TEAE did not appear to be related to dose at onset (Table 4).

A higher proportion of patients taking at least one concomitant SCB AED at Baseline reported a TEAE (29/30 [96.7%]) compared with those not on concomitant SCB AEDs (13/17 [76.5%]) (Supplementary Table 1).

Twenty patients (42.6%) exited the trial due to TEAEs, most commonly vomiting (4/47 [8.5%]), gait disturbance, dizziness, or somnolence (all 3/47 [6.4%] each), most of which (18/20 [90.0%]) were considered related to trial medication. A higher incidence of TEAEs, and TEAEs leading to trial exit, was observed among patients 12–17 years of age compared with younger patients. Of the seven patients who did not continue in the extension trial, five chose not to continue due to a TEAE (one each of “drug-induced liver injury” [reported term after

Table 3
Treatment-emergent adverse events (SS).

	≥1 month to < 4 years (*n* = 15)	≥4 to ≤17 years			All patients ≥1 month to ≤17 years (*n* = 47)
		≥4 to < 12 years (*n* = 23)	≥12 to ≤17 years (*n* = 9)	Combined ≥4 to ≤17 years (*n* = 32)	
Patients experiencing ≥1 TEAE, *n* (%)					
	14 (93.3)	19 (82.6)	9 (100.0)	28 (87.5)	42 (89.4)
TEAEs occurring in ≥10% of all patients, *n* (%)					
Vomiting	1 (6.7)	7 (30.4)	2 (22.2)	9 (28.1)	10 (21.3)
Diarrhea	2 (13.3)	4 (17.4)	1 (11.1)	5 (15.6)	7 (14.9)
Somnolence	2 (13.3)	3 (13.0)	1 (11.1)	4 (12.5)	6 (12.8)
Irritability	3 (20.0)	1 (4.3)	1 (11.1)	2 (6.3)	5 (10.6)
Dizziness	0	3 (13.0)	2 (22.2)	5 (15.6)	5 (10.6)
Pyrexia	2 (13.3)	3 (13.0)	0	3 (9.4)	5 (10.6)
Patients experiencing ≥1 lacosamide-related TEAE, *n* (%)					
	6 (40.0)	14 (60.9)	8 (88.9)	22 (68.8)	28 (59.6)
TEAEs considered to be lacosamide-related and occurring in ≥5% of all patients, *n* (%)					
Vomiting	1 (6.7)	3 (13.0)	2 (22.2)	5 (15.36)	6 (12.8)
Dizziness	0	3 (13.0)	2 (22.2)	5 (15.6)	5 (10.6)
Somnolence	2 (13.3)	1 (4.3)	1 (11.1)	2 (6.3)	4 (8.5)
Irritability	2 (13.3)	1 (4.3)	1 (11.1)	2 (6.3)	4 (8.5)
Gait disturbance	0	2 (8.7)	1 (11.1)	3 (9.4)	3 (6.4)
Patients discontinuing because of TEAEs, *n* (%)					
	5 (33.3)	9 (39.1)	6 (66.7)	15 (46.9)	20 (42.6)
TEAEs leading to discontinuation of ≥5% of all patients					
Vomiting	0	2 (8.7)	2 (22.2)	4 (12.5)	4 (8.5)
Gait disturbance	0	2 (8.7)	1 (11.1)	3 (9.4)	3 (6.4)
Dizziness	0	1 (4.3)	2 (22.2)	3 (9.4)	3 (6.4)
Somnolence	1 (6.7)	2 (8.7)	0	2 (6.3)	3 (6.4)
Patients experiencing serious TEAEs, *n* (%)					
Any	3 (20.0)	3 (13.0)	0	3 (9.4)	6 (12.8)
Status epilepticus[a]	2 (13.3)	1 (4.3)	0	1 (3.1)	3 (6.4)

SS, Safety Set; TEAE, treatment-emergent adverse event.
TEAEs reported as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.
[a] Two cases (patients of 1 year and 4 years of age, respectively) were considered by the investigator to be related to lacosamide treatment.

finding of elevated transaminases; considered lacosamide-related; however, bilirubin was normal; see below for further details], rash, aggression, dizziness, and status epilepticus), one chose not to continue due to lack of efficacy, and one because of personal choice (Fig. 1). A higher proportion of patients with a concomitant SCB AED at Baseline exited the trial due to a TEAE (15/30 [50.0%]) compared with those not taking concomitant SCB AEDs (5/17 [29.4%]).

Six patients experienced a single serious TEAE: status epilepticus (*n* = 3), viral pneumonia, viral upper respiratory tract infection, and dehydration (*n* = 1 each). Among the three patients reporting status epilepticus, one (aged 2 years) experienced status epilepticus that was considered severe in intensity, which resolved after 1 day. This TEAE was considered related to lacosamide and led to the patient exiting the trial. The two other patients (aged 4 years and 1 year, respectively) experienced status epilepticus that was not considered to be lacosamide-related, and of mild or moderate intensity. No other seizure-related TEAEs of any intensity were reported.

No consistent or clinically relevant changes from Baseline were reported for hematology, clinical chemistry, endocrinology, or urinalysis parameters. There was no evidence for any consistent effect on vital signs, 12-lead ECG recordings, or physical examinations. One patient, aged 2 years with a history of elevated liver enzymes, reported transiently elevated transaminases and alkaline phosphatase with normal bilirubin 1 day after discontinuing lacosamide. This TEAE was recorded as the reason for trial discontinuation and was considered to be lacosamide-related and of moderate intensity. This TEAE was not considered serious and resolved after 29 days. Nine patients had clinically significant treatment-emergent neurological examination abnormalities: "general" abnormalities (level of consciousness, speech, or mental status) in three patients (1, 10, and 12 years of age); cranial nerve abnormalities in two patients (5 and 15 years of age; cranial nerve V associated abnormalities: jaw movement/facial sensation, and cranial nerve VIII associated abnormalities: hearing, respectively); bilateral rapid alternating movements, abnormal muscle strength in the upper extremities, abnormal plantar reflex, and cranial nerve VII abnormalities (facial motion) in one patient (7 years of age); coordination (gait, Romberg stance, vertical nystagmus), overall movement and general abnormalities in one patient (5 years of age); abnormal gait, abnormal muscle tone, and general abnormalities in one patient (7 years of age); and bilateral tremor in another patient (4 years of age).

Table 4
Treatment-emergent adverse events by dose at onset (SS).

	Dose at onset							All patients (*n* = 47)
	1 mg/kg/day (*n* = 2)	2 mg/kg/day (*n* = 47)	4 mg/kg/day (*n* = 47)	6 mg/kg/day (*n* = 46)	8 mg/kg/day (*n* = 42)	10 mg/kg/day (*n* = 28)	12 mg/kg/day (*n* = 21)	
Age group ≥1month to ≤4 years								
Patients experiencing ≥1 TEAE, *n* (%)								
	0	8 (17.0)	6 (12.8)	6 (13.0)	7 (16.7)	2 (7.1)	1 (4.8)	14 (29.8)
TEAEs occurring in ≥5% of all patients, *n* (%)								
Irritability	0	1 (2.1)	2 (4.3)	0	0	0	0	3 (6.4)
Pharyngotonsillitis	0	2 (4.3)	0	0	1 (2.4)	0	0	3 (6.4)
Age group ≥4 to < 12 years								
Patients experiencing ≥1 lacosamide-related TEAE, *n* (%)								
	2 (100)	9 (19.1)	7 (14.9)	6 (13.0)	7 (16.7)	8 (28.6)	4 (19.0)	19 (40.4)
TEAEs occurring in ≥5% of all patients, n (%)								
Vomiting	1 (50.0)	0	1 (2.1)	2 (4.3)	0	1 (3.6)	1 (4.8)	6 (12.8)
Diarrhea	0	1 (2.1)	2 (4.3)	1 (2.2)	1 (2.4)	1 (3.6)	0	4 (8.5)
Pyrexia	0	0	1 (2.1)	0	1 (2.4)	2 (7.1)	0	3 (6.4)
Dizziness	0	1 (2.1)	0	2 (4.3)	0	0	1 (4.8)	3 (6.4)
Somnolence	0	0	0	0	1 (2.4)	2 (7.1)	0	3 (6.4)
Age group ≥12 to ≤17 years[a]								
Patients experiencing ≥1 lacosamide-related TEAE, *n* (%)								
	0	5 (10.6)	5 (10.6)	4 (8.7)	3 (7.1)	3 (10.7)	0	9 (19.1)

TEAE, treatment-emergent adverse event.
TEAEs reported as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.
[a] No TEAE was experienced by ≥5% of patients of ≥12 to ≤17 years of age.

No cardiac-related TEAEs were reported. Overall, a median increase in PR interval from Baseline of 6.4 ms (range -16.5–28.2 ms) was observed by the last visit. This increase was most pronounced but was not considered clinically relevant in patients aged 12–17 years; median 16.5 ms (range -6.4–28.2 ms, $n = 9$), vs. 6.3 ms (-14.5–15.8 ms, $n = 15$) in patients < 4 years, and 6.4 ms (-16.5–17.3 ms, $n = 23$) in patients 4–12 years of age. Post-Baseline PR intervals for all patients, at all visits, ranged from 82.0 to 212.0 ms.

3.5. Exploratory efficacy outcomes

Although this trial was neither designed nor powered to assess efficacy, all age groups showed a small median percent reduction in overall seizure frequency per 28 days from Baseline to the Treatment Period (Supplementary Table 2; FAS). Overall, the proportion of patients achieving ≥50% reduction in focal seizure frequency per 28 days from Baseline to the end of treatment was 21.7% (10/46 patients, FAS), while 13.0% (6/46 patients) achieved a ≥75% reduction. Conversely, 23.9% (11/46) of patients experienced no change in seizure frequency, and 39.1% (18/46) experienced an increase in seizure frequency.

The median percent reduction in seizure frequency per 28 days was lower among patients who took concomitant SCB AEDs at Baseline, compared with those not on concomitant SCB AEDs (-7.43% [range -100–320%], $n = 30$ vs. -14.27% [range -89.5–242.3%], $n = 16$). The proportion of patients with a ≥50% reduction in seizure frequency per 28 days was also lower in patients with concomitant SCB AEDs, compared with those not on SCB AEDs (16.7% [5/30] vs. 31.3% [5/16]) (no change: 26.7% [8/30] vs. 18.8% [3/16]) (≥25% increase: 40.0% [12/30] vs. 37.5% [6/16]).

The majority of patients had an overall improvement in their condition, as assessed by the CGI-C (38/45 [84.4%]) and the CaGI-C (38/44 [86.4%]) (Supplementary Table 2).

4. Discussion

This prospective, short-term (maximum duration of 13 weeks), fixed-titration trial evaluated the safety and tolerability of lacosamide oral solution added to one to three concomitant AEDs for the treatment of focal seizures in children. The trial results and PK modeling [27] provided valuable insight into the most appropriate dosage regimens for the phase II/III trials of adjunctive lacosamide therapy in pediatric patients with epilepsy (SP0966, NCT01969851; SP0967, NCT02477839; SP0969, NCT01921205; SP0982, NCT02408523). The ongoing long-term extension trial (SP848; NCT00938912) allows flexible dosing of lacosamide and concomitant AEDs and is expected to enroll a further 250 patients, providing additional clinical data on the tolerability of lacosamide in the pediatric epilepsy population.

Although children aged 1 month to 17 years were eligible to participate in the current trial, no patients aged < 6 months were enrolled. Patients had a mean epilepsy duration of 4 years, with a median of 11 focal seizures per 28 days at Baseline. The observed TEAE profile of adjunctive lacosamide in patients aged 6 months to 17 years with focal seizures was generally consistent with that reported for adults [10–12]. No new safety concerns were identified, and there was no indication of a dose-dependent effect on the incidence of TEAEs. Per the protocol, patients who reached a maximum tolerated dose that was below the cohort-defined maximum (i.e., required a dose reduction) were discontinued, which contributed to the high trial discontinuation rate of 48.9%. However, 40/47 (85.1%) patients chose to continue with lacosamide treatment by entering the extension trial. Of the seven patients who did not plan to continue lacosamide, four discontinued due to developing a TEAE listed in the lacosamide prescribing information [8,9], one due to status epilepticus, one due to a lack of efficacy, and the other by personal choice.

In a systematic review of retrospective and prospective cohort studies, series, and case reports assessing lacosamide in patients < 21 years of age, adverse events were reported in 18–59% of patients with drug-resistant epilepsy [31]. The most common AEs were dizziness, sedation, gastrointestinal upset, and mood and behavioral changes. The current trial builds on these findings by assessing the safety and tolerability of adjunctive lacosamide when administered in a structured and controlled titration pattern, to pediatric patients with a diverse age range and a single type of seizure (focal). However, this fixed-titration schedule may have contributed to the observed high incidence of TEAEs (89.4%). With one exception of status epilepticus, all TEAEs reported were mild or moderate in intensity, with the most common being vomiting, diarrhea, and somnolence. Status epilepticus was reported by three patients. The lack of placebo or control groups prevented comparison of the incidence of status epilepticus with alternative therapies, or as part of the natural course of the disease.

A subsequent phase III, double-blind, placebo-controlled trial (SP0969) evaluated efficacy and tolerability of adjunctive lacosamide in children and adolescents aged ≥4 to < 17 years with uncontrolled focal seizures [25,26]. In contrast to the current trial, in which lacosamide doses were increased via fixed titration to the patient's maximum tolerated/recommended dose, the double-blind trial had a flexible titration schedule with dose-holds and back-titration permitted as needed to improve tolerability. Lower incidences of TEAEs and drug-related TEAEs were observed with lacosamide in the double-blind trial compared with the current fixed-titration trial. The incidence of TEAEs was higher during Titration than Maintenance, and few patients (4%) discontinued due to TEAEs. Together, the results from the two trials suggest that flexible dosing according to individual patient needs may help to maximize tolerability of lacosamide in children. An analysis of interim data from several open-label trials in children (aged 4 to < 16 years) with focal seizures indicated that adjunctive lacosamide is generally well tolerated during long-term treatment (49% of patients had > 12 months exposure) [32].

As per current prescribing information and a review of cardiac safety [33], lacosamide should be used with caution in patients with underlying proarrhythmic conditions, such as cardiac conduction problems, severe cardiac disease, or cardiac sodium channelopathies [33,34]. Lacosamide should also be used with caution in patients taking concomitant medications affecting cardiac conduction, including sodium channel blockers and medications that prolong the PR interval [33,34]. Underlying proarrhythmic conditions are generally more prevalent in older patients than in children. Per the trial protocol, children with a clinically relevant ECG abnormality, hemodynamically significant heart disease, arrhythmic heart condition requiring medical therapy, or known sodium channelopathy were excluded. A small increase in PR interval was observed, consistent with that see in adults on lacosamide [33]. The increase was not considered clinically relevant, and no cardiac-related TEAEs were reported.

This trial was designed to assess tolerability and as such, specific elements of its design (open-label, small sample size, short treatment duration with few days at maximum dose, use of historical seizure data for Baseline values) preclude meaningful conclusions regarding efficacy. Nonetheless, 22% of patients had a ≥50% reduction in seizure frequency, and the majority (> 80%) of treating physicians and caregivers felt that lacosamide had been beneficial for their patients as assessed by CGI-C and CaGI-C questionnaires. In line with these results, a phase III, double-blind, placebo-controlled trial has demonstrated that adjunctive lacosamide is efficacious in reducing seizure frequency in children and adolescents with uncontrolled focal seizures [25,26].

In the current trial, pediatric patients who took concomitant SCB AEDs at Baseline reported a slightly higher incidence of TEAEs, and slightly poorer efficacy responses compared with those not taking SCB AEDs. However, these findings are difficult to interpret given the small sample size and imbalance in the number of patients in each subgroup. Almost twice as many patients were taking concomitant SCB AEDs ($n = 30$) than non-SCB AEDs ($n = 17$) at Baseline. The higher incidence of TEAEs observed in patients taking concomitant SCB AEDs compared

with those not taking SCB AEDs may not be completely unexpected because of the combined targeting of the voltage-gated sodium channels. In a retrospective cohort study in children with focal, generalized, or mixed seizure types, TEAEs were reported more often in patients taking concomitant SCB AEDs than those not taking SCB AEDs [35]. Furthermore, a post hoc analysis of a placebo-controlled, double-blind trial showed a higher incidence of drug-related TEAEs with lacosamide in children and adolescents taking concomitant SCB AEDs compared with those not taking SCB AEDs [36]. Data in adults have shown inconsistent findings on tolerability and efficacy of lacosamide with or without concomitant SCB AEDs [37–46].

5. Conclusion

The results from this prospective, phase II, open-label, fixed-titration trial support the safety and tolerability of adjunctive lacosamide at doses up to 12 mg/kg/day in pediatric patients (aged 6 months to 17 years) with focal seizures. The observed TEAE profile was generally consistent with that observed during trials of adjunctive lacosamide in adult patients, with no new safety concerns identified and no observed relationship between the lacosamide dose and the incidence of TEAEs. A more flexible titration scheme may improve tolerability.

Disclosure of conflicts of interest

This trial was funded by UCB Pharma. The sponsor was responsible for the design of the trial and the analyses of data collected by the investigators. Data were interpreted by the authors and the sponsor. The sponsor was involved in the review of the manuscript and the decision to submit for publication. All authors approved the final version of the manuscript for publication. Jose A. Ferreira has received research funding from UCB Pharma. Ahmed T. Abdelmoity has participated in speakers' bureaus for Lundbeck, Livanova, and Supernus. Jean-Baptiste Le Pichon has no conflicts of interest. Tony Daniels and William Byrnes are employees of UCB Pharma. Deanne Dilley and Peter Dedeken were employees of UCB Pharma at the time this trial was conducted.

Transparency document

The Transparency document associated with this article can be found in the online version.

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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.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2019.05.016.

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