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Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials

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ABSTRACT

Objective: The objective of this study was to describe *a priori* protocol-defined analyses to evaluate the safety and tolerability of adjunctive oral lacosamide (200–600 mg/day) in adults (ages 16–70 years) with partial-onset seizures (POS) using data pooled from three similarly designed randomized, double-blind, placebo-controlled trials (SP667, SP754 [NCT00136019], SP755 [NCT00220415]).
Methods: Patients with POS (≥2 years' duration, ≥2 previous antiepileptic drugs [AEDs]) uncontrolled by a stable dosing regimen of 1–3 concomitant AEDs were randomized to treatment with lacosamide at doses of 200 mg/day, 400 mg/day, or 600 mg/day, or placebo. Studies comprised a 4- to 6-week titration phase to target dose followed by a 12-week maintenance phase. Safety outcomes included treatment-emergent adverse events (TEAEs) of particular relevance to patients with POS, overall TEAEs, and discontinuations due to TEAEs. *Post hoc* analyses included evaluation of TEAEs potentially related to cognition and TEAEs leading to discontinuation analyzed by concomitant AEDs.
Results: One thousand three hundred eight patients were randomized to and received treatment; 944 to lacosamide and 364 to placebo. Most patients (84.4%) were taking 2 or 3 concomitant AEDs. The most common drug-associated TEAEs (reported by ≥5% of patients in any lacosamide dose group and with an incidence at least twice that reported for placebo during the treatment phase) were dizziness (30.6% for lacosamide *vs* 8.2% for placebo), nausea (11.4% *vs* 4.4%), and diplopia (10.5% *vs* 1.9%). Common drug-associated TEAEs generally appeared to be dose-related, and the incidence of each was lower during the 12-week maintenance phase than during the titration phase. Most TEAEs were either mild or moderate in intensity; severe TEAEs were predominantly observed with lacosamide 600 mg/day. No individual serious TEAE occurred in ≥1% of all lacosamide-treated patients. Treatment-emergent adverse events led to discontinuation in 8.1%, 17.2%, and 28.6% of the lacosamide 200-, 400-, and 600-mg/day groups, respectively (*vs* 4.9% of placebo). Few TEAEs were related to rash, weight loss/gain, changes in clinical chemistry parameters, or psychiatric disturbances, or were seizure-related. The odds of reporting any potential cognition-related TEAE *vs* placebo increased with dose and were similar between lacosamide doses of 200 and 400 mg/day and placebo (odds ratio 1.3, 95% confidence interval 0.7–2.4). Discontinuations due to TEAEs based on most commonly used AEDs taken in combination with lacosamide (all doses combined) were carbamazepine (15.3% [51/334] *vs* 3.9% [5/129] placebo), lamotrigine (19.2% [56/291] *vs* 4.3% [5/117]), and levetiracetam (10.1% [28/278] *vs* 3.9% [4/103]).
Conclusions: The safety and tolerability profile of adjunctive lacosamide in this detailed evaluation was similar to that observed in the individual double-blind trials. Adjunctive lacosamide was associated with TEAEs related to the nervous system and gastrointestinal tract, predominantly during titration.

1. Introduction

The antiepileptic drug (AED) lacosamide is approved at dosages up to 400 mg/day as monotherapy or adjunctive therapy in adults (17 years or older) with partial-onset seizures (POS) in the United States [1] and as adjunctive therapy in adults (16 years or older) with POS in the European Union [2] and other countries. Lacosamide has simple pharmacokinetics for oral and intravenous administration [3–6].

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Orally administered lacosamide is rapidly and completely absorbed with steady-state plasma levels occurring after 3 days of twice-daily administration [3]. The pharmacokinetic parameters of lacosamide are dose-proportional (orally administered 100–800 mg/day) and show low intra- and intersubject variability [3]. Lacosamide is minimally bound to plasma proteins (<15%) [4,7] and is eliminated from the systemic circulation primarily by renal excretion [3]. Lacosamide has shown no clinically relevant drug–drug interactions with other AEDs [8–13], midazolam [2,14], warfarin [15], oral contraceptives [16], omeprazole [17], digoxin [18], and metformin [19].

The safety and efficacy of lacosamide as adjunctive therapy for adults with POS have been evaluated in detail, including in three phase II/III randomized, double-blind, placebo-controlled clinical trials and their respective long-term open-label extension trials [10–12,20,21]. Results from these pivotal double-blind trials demonstrated that adjunctive lacosamide significantly reduced the frequency of POS in patients with epilepsy and was associated with an acceptable safety profile [10–12]. However, the evaluation of drug safety is a continuous process and depends on input from various sources, including standard registration trials, long-term extension studies, observational studies, and safety monitoring efforts. Pooled data analyses from multiple clinical trials are another means to assess drug safety.

The three double-blind lacosamide trials had similar study designs and patient populations, thus, allowing a valuable opportunity for data pooling. The pooling of data from the three trials facilitates a more detailed evaluation of treatment effect than that from individual trials. Efficacy analyses on pooled data are published [22], confirming and extending the results of the individual trials. Notably, adjunctive lacosamide significantly reduced overall seizure frequency compared with placebo treatment, regardless of concomitant AEDs or patients' epilepsy surgical history [22]. An additional *post hoc* analysis suggested that adjunctive lacosamide treatment demonstrated seizure reduction compared with placebo regardless of the inclusion of "traditional" sodium channel blockers, which were included in the concomitant AED regimen of 82% of patients [23]. This *post hoc* analysis also showed that lacosamide was well tolerated by most patients taking either sodium channel-blocking AEDs or nonsodium channel-blocking AEDs and suggested that lacosamide may have potential for improved tolerability when added to an AED regimen that did not include traditional sodium channel blockers, especially at higher lacosamide doses [23].

Here, we present the results of *a priori* protocol-defined and *post hoc* safety analyses of data pooled from the three pivotal double-blind, placebo-controlled lacosamide trials. Though data have been reported elsewhere [22–24], the current analyses go beyond previous reports to provide a more detailed description of the safety profile of lacosamide, including additional safety information of particular interest, such as rash, psychiatric effects, seizure-related adverse events (AEs), weight change, and clinical laboratory changes. In addition, *post hoc* analyses investigated AEs potentially related to cognition and AEs leading to discontinuation analyzed by concomitant AEDs.

2. Methods

2.1. Trial design

Safety analyses were performed on data pooled from three similarly designed randomized, double-blind, placebo-controlled trials (SP667 [10], SP754 [NCT00136019] [11] and SP755 [NCT00220415] [12]) that evaluated the safety and efficacy of adjunctive lacosamide treatment in adults with uncontrolled POS. The SP667 trial was conducted in Europe and the United States, SP754 in the United States, and SP755 in Europe and Australia. Detailed methods are published elsewhere [10–12]. All studies were conducted in accordance with the Declaration of Helsinki. The trial protocol, amendments, and informed consent documentation were reviewed by national regulatory authorities in each country and relevant ethics committees or Institutional Review Boards for each site. Before trial participation, all patients gave written informed consent.

In each trial, patients were randomized to receive fixed dosages of lacosamide or placebo twice-daily in equally divided doses (Fig. 1). In all trials, a single 100 mg/day dose reduction was allowed at the end of the titration phase for patients experiencing intolerable AEs.

2.2. Patient eligibility

Patients aged 16–70 years (18–65 years in SP667) with a diagnosis of focal epilepsy and who had experienced POS (with or without secondary generalization) for 2 years or longer despite therapy with two or more AEDs (concurrently or sequentially) were recruited. To be eligible for randomization, patients were required to have an average

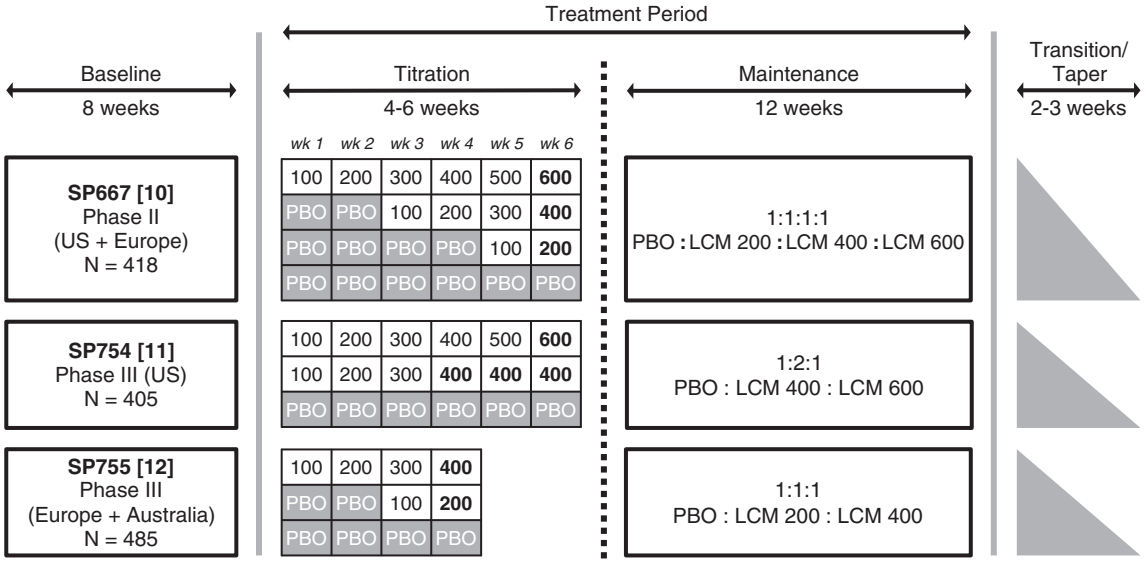

Fig. 1. Design of the double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures. One back-titration of 100 mg/day was allowed at the end of titration in cases of intolerable adverse events. PBO, placebo; LCM, lacosamide.
Modified from Chung S. et al. [22].

of at least four POS (simple partial with motor signs, complex partial, or secondarily generalized seizures) per 28 days, with seizure-free periods lasting no longer than 21 days, in the 8 weeks prior to baseline and during the 8-week baseline period. Patients had to be receiving a stable dosing regimen of 1–3 concomitant AEDs (no more than two in SP667) with or without vagus nerve stimulation for at least 4 weeks prior to baseline and throughout the trial.

2.3. Safety assessments

Safety variables were treatment-emergent adverse events (TEAEs) as reported during the titration, maintenance, and treatment (titration + maintenance) phases, serious TEAEs (SAEs; those TEAEs that were fatal or life-threatening, required or prolonged hospitalization, were a congenital anomaly/birth defect, or were considered to be an important medical event that may have jeopardized the patient or put them at risk), and TEAEs leading to discontinuation. In addition, TEAE severity (intensity, which ranged from mild [did not interfere with routine activities] to severe [subject was unable to perform routine activities]) and relationship to trial medication, as judged by the investigator, were also evaluated.

The definition of a TEAE used in the trials was consistent with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. The TEAEs (observed by the investigator or reported by the patient to the investigator) were collected at each clinical visit and were coded according to Medical Dictionary for Regulatory Activities (MedDRA, version 9.1) preferred terms and the corresponding primary system organ class. In order to standardize investigator evaluation of safety among sites and trials, standard assessments were described for seriousness, intensity, outcome, and causality. An AE was defined as treatment-emergent if it started on or after the date of the first dose of trial medication. A TEAE that first occurred during the titration phase (whether or not it persisted throughout the maintenance phase) was included only for the incidence of TEAEs during the titration phase, while a TEAE that occurred only during the maintenance phase was included only for the incidence of TEAEs during this phase. If a TEAE started during the titration phase, resolved in the maintenance phase, and then reemerged as a new event during maintenance phase, the event was included in the TEAE incidence for both phases.

To further evaluate TEAEs associated with lacosamide, common drug-associated TEAEs were defined as those reported by ≥5% of patients in any lacosamide dose group and with an incidence at least twice that reported for placebo during the treatment phase. The TEAEs related to rash, psychiatric disturbances (psychosis, depression, and suicide), weight change, cognition, or seizures were also assessed. Laboratory parameters, ECGs, vital signs, and body weight were also monitored.

2.4. Data analyses

Pooled analyses of safety variables were performed on the safety set, which included all patients who took at least one dose of trial medication (lacosamide or placebo) during one of the three double-blind trials. Results were summarized using descriptive statistics.

For the evaluation of TEAEs related to rash, the following four MedDRA preferred terms were evaluated: rash, rash pruritic, rash generalized, and rash maculopapular. For the assessment of select psychiatric events, the following three MedDRA preferred terms were evaluated for TEAEs related to psychosis: psychotic disorder, epileptic psychosis, and acute psychosis. The following three MedDRA preferred terms were evaluated for TEAEs related to suicide: suicidal ideation, suicide attempt, and completed suicide. The MedDRA preferred term depression was analyzed separately. For TEAEs related to seizure, the following 10 MedDRA preferred terms were examined: convulsion, grand mal convulsion, epilepsy, aura, epileptic aura, simple partial seizures, complex partial seizures, partial seizures, myoclonus, and status epilepticus.

For TEAEs potentially related to cognition, the following 17 MedDRA preferred terms were identified: memory impairment, cognitive disorder, confusional state, disturbance in attention, mental impairment, lethargy, bradyphrenia, amnesia, mental status changes, disorientation, aphasia, depressed level of consciousness, communication disorder, dissociation, speech disorder, dysphasia, and reading disorder. As testing group differences for these specific terms was not prespecified in the studies, a *post hoc* analysis comparing treatment to placebo was performed to evaluate this broad range of terms. The incidence of individual TEAEs was calculated for each lacosamide dose group (combined and separate) and for placebo, and the odds of experiencing any TEAEs identified as cognition-related were evaluated using a logistic regression model with adjustment for trial.

An analysis was also performed to evaluate TEAEs that led to discontinuation, according to concomitant AED use. In this analysis, patients could be assigned to as many as three different subgroups (one for each concomitant AED taken). The TEAEs that led to discontinuation were assessed for all lacosamide doses combined and for placebo.

3. Results

3.1. Demographic and baseline characteristics in the pooled patient population

The pooled safety population included 1308 patients who received at least one dose of trial medication during the double-blind trials (safety set; Fig. 2). Of these patients, 944 received lacosamide (200 mg/day, n = 270; 400 mg/day, n = 471; 600 mg/day, n = 203) and 364 received placebo. Mean age was 38.6 ± 11.79 years, and there was an even distribution of men (49.0%) and women (51.0%) (Table 1). Of 1308 patients, 587 (44.9%) had lifetime use of ≥7 AEDs; most patients (84.4%) were taking 2–3 concomitant AEDs, primarily carbamazepine (35.4%), lamotrigine (31.2%), and levetiracetam (29.1%) (groups not mutually exclusive). Patients experienced a median of 11.5 seizures per 28 days during the 8-week baseline.

3.2. Patient disposition

Most patients (78.5%) completed the trial in which they enrolled. Among patients assigned to lacosamide, completer rates were 81.9% (200 mg/day), 77.1% (400 mg/day), and 61.2% (600 mg/day), compared with 87.1% of patients assigned to placebo (Fig. 2). The percentage of patients discontinuing from the trial because of AEs increased with increasing lacosamide dose (9.6% for lacosamide 200 mg/day, 17.2% for 400 mg/day, and 28.6% for 600 mg/day); in the placebo group, 5.2% of patients discontinued because of AEs. Other reasons for discontinuation (lack of efficacy, withdrew consent, protocol deviation, poor compliance, and lost to follow-up) occurred at similar rates across lacosamide and placebo treatments. Of 1308 patients in the safety set, 1054 (80.6%) enrolled in the subsequent lacosamide open-label extension trials.

3.3. Overall incidence of TEAEs

During the treatment phase (titration + maintenance), the overall incidence of any TEAE was 81.0% for all lacosamide doses combined (*vs* 64.6% for placebo) and appeared to be dose-related (69.6% for 200 mg/day, 82.2% for 400 mg/day, and 93.6% for 600 mg/day). Among all patients who received lacosamide, the most frequently reported TEAEs (occurring at an incidence of ≥10%) were dizziness (30.6% *vs* 8.2% for placebo), headache (12.7% *vs* 8.8%), nausea (11.4% *vs* 4.4%), and diplopia (10.5% *vs* 1.9%). Of these, dizziness, nausea, and diplopia were among those considered drug-associated TEAEs (occurring in ≥5% of patients in any lacosamide treatment group and at least twice as often as in the placebo group; Table 2). Common drug-associated TEAEs were most commonly associated with the

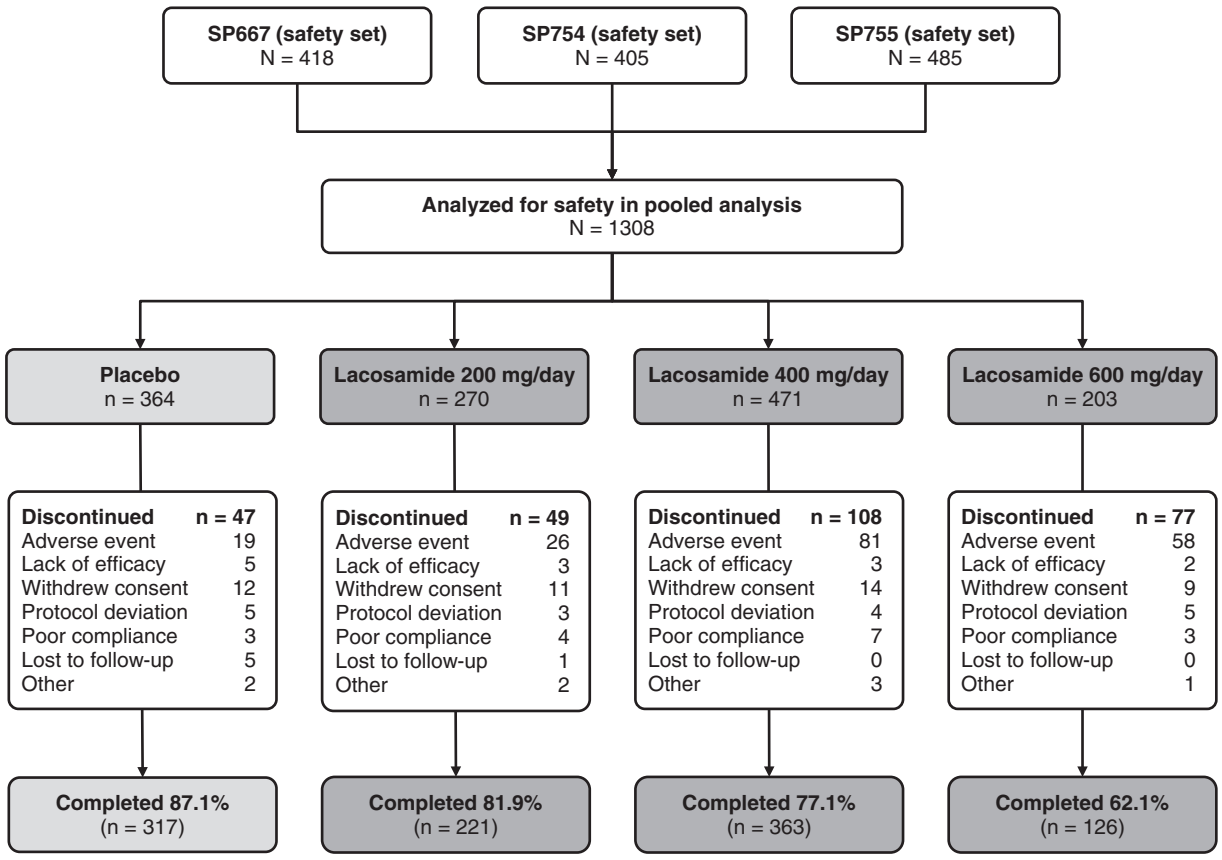

Fig. 2. Patient disposition in the pooled analysis of double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures. Modified from Chung S. et al. [22].

nervous system (40.3%), and all appeared to be dose-related (Table 2). Incidence of TEAEs considered by the investigator to be related to trial medication was 61.1% for lacosamide overall and increased with increasing lacosamide dose: 44.1% for lacosamide 200 mg/day, 62.8% for lacosamide 400 mg/day, and 79.8% for lacosamide 600 mg/day, compared with 38.7% for placebo. For the approved lacosamide dose range

Table 1
Demographic and baseline characteristics of patients participating in double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures (safety set).

	Placebo (n = 364)	Adjunctive lacosamide			Total population (N = 1308)
		200 mg/day (n = 270)	400 mg/day (n = 471)	600 mg/day (n = 203)	
Age (mean ± SD, years)	38.5 ± 11.25	38.1 ± 11.78	39.2 ± 12.44	38.1 ± 11.18	38.6 ± 11.79
Female, n (%)	177 (48.6)	134 (49.6)	245 (52.0)	111 (54.7)	667 (51.0)
Time since diagnosis, (mean ± SD, years)[a]	23.3 ± 12.56	23.7 ± 12.56	24.0 ± 13.14	23.5 ± 12.97	23.7 ± 12.82
Lifetime AEDs, n (%)					
1–3	80 (22.0)	62 (23.0)	112 (23.8)	32 (15.8)	286 (21.9)
4–6	121 (33.2)	84 (31.1)	151 (32.1)	68 (33.5)	424 (32.4)
≥7	160 (44.0)	120 (44.4)	205 (43.5)	102 (50.2)	587 (44.9)
Missing	3 (0.8)	4 (1.5)	3 (0.6)	1 (0.5)	11 (0.8)
Number of concomitant AEDs, n (%)					
1	62 (17.0)	34 (12.6)	78 (16.6)	30 (14.8)	204 (15.6)
2	214 (58.8)	168 (62.2)	281 (59.7)	151 (74.4)	814 (62.2)
3[b]	88 (24.2)	68 (25.2)	112 (23.8)	22 (10.8)	290 (22.2)
Most common[c] concomitant AEDs, n (%)					
Carbamazepine	129 (35.4)	115 (42.6)	150 (31.8)	69 (34.0)	463 (35.4)
Lamotrigine	117 (32.1)	70 (25.9)	159 (33.8)	62 (30.5)	408 (31.2)
Levetiracetam	103 (28.3)	70 (25.9)	147 (31.2)	61 (30.0)	381 (29.1)
Valproate	95 (26.1)	74 (27.4)	99 (21.0)	40 (19.7)	308 (23.5)
Topiramate	83 (22.8)	70 (25.9)	106 (22.5)	32 (15.8)	291 (22.2)
Median baseline seizure frequency per 28 days[d]	11.0	12.2	11.0	13.5	11.5

AEDs, antiepileptic drugs.
[a] n = 470 for 400 mg/day, 202 for 600 mg/day, and 1306 for total population.
[b] Trial SP667 did not allow patients taking three concomitant AEDs.
[c] Represents the five most commonly used concomitant AEDs.
[d] n = 359 for placebo, 267 for 200 mg/day, 469 for 400 mg/day, 202 for 600 mg/day, and 1297 for total population.

Table 2
Incidence of common drug-associated TEAEs[a] during the treatment phase (titration and maintenance) in double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures (safety set).

MedDRA preferred term	Placebo (n = 364)	Adjunctive lacosamide			
		200 mg/day (n = 270)	400 mg/day (n = 471)	600 mg/day (n = 203)	All doses of lacosamide (n = 944)
Dizziness	30 (8.2)	43 (15.9)	139 (29.5)	107 (52.7)	289 (30.6)
Nausea	16 (4.4)	20 (7.4)	53 (11.3)	35 (17.2)	108 (11.4)
Diplopia	7 (1.9)	17 (6.3)	49 (10.4)	33 (16.3)	99 (10.5)
Vomiting	9 (2.5)	16 (5.9)	40 (8.5)	32 (15.8)	88 (9.3)
Fatigue	21 (5.8)	19 (7.0)	34 (7.2)	30 (14.8)	83 (8.8)
Vision blurred	9 (2.5)	6 (2.2)	40 (8.5)	33 (16.3)	79 (8.4)
Ataxia[b]	6 (1.6)	11 (4.1)	34 (7.2)	31 (15.3)	76 (8.1)
Tremor	15 (4.1)	10 (3.7)	29 (6.2)	24 (11.8)	63 (6.7)
Nystagmus	14 (3.8)	6 (2.2)	21 (4.5)	21 (10.3)	48 (5.1)
Balance disorder	0 (0)	3 (1.1)	24 (5.1)	13 (6.4)	40 (4.2)
Memory impairment	6 (1.6)	3 (1.1)	7 (1.5)	12 (5.9)	22 (2.3)

MedDRA, Medical Dictionary for Regulatory Activities.
For each TEAE, data are presented as n (%) of patients experiencing the TEAE at least once.
[a] Common drug-associated TEAEs defined as those TEAEs occurring in ≥5% of patients in any lacosamide treatment group and at least twice as often as in the placebo group.
[b] Reported as coordination abnormal.

(200–400 mg/day), the only TEAEs that occurred with an incidence of ≥10% were dizziness (24.6%) and headache (12.8%).

3.4. Intensity of TEAEs

Most patients who received lacosamide reported TEAEs with a maximum intensity of mild (32.2%) or moderate (38.3%) (*vs* placebo: 38.5% mild, 21.4% moderate). Severe TEAEs were reported by 10.4% of patients in the lacosamide group, and 4.7% of those receiving placebo. Incidences of severe TEAEs were similar in the lacosamide 200 mg/day (7.0%) and 400 mg/day (9.1%) groups, but increased with lacosamide 600 mg/day (17.7%). The most frequently reported severe common drug-associated TEAE overall was dizziness (3.7% for lacosamide *vs* 0% for placebo) and increased across the lacosamide dose range (1.9% for 200 mg/day, 2.3% for 400 mg/day, and 9.4% for 600 mg/day). Incidence of all other common drug-associated TEAEs rated as severe did not increase in a dose-dependent manner.

3.5. TEAEs during titration vs maintenance

Overall, 68.3% of patients in the lacosamide group and 53.3% of placebo patients reported at least one TEAE during the titration phase (4–6 weeks, depending on study). The incidence of TEAEs during the titration phase increased with increasing lacosamide dose: 51.1% for lacosamide 200 mg/day, 69.9% for 400 mg/day, and 87.7% for 600 mg/day. During the maintenance phase, at least one TEAE was reported by 60.2% (470/781) of patients who received lacosamide during the phase and 44.5% (150/337) of those who received placebo during the phase. Incidence of TEAEs during the maintenance phase was generally similar across lacosamide dose groups (54.9% [135/246] for 200 mg/day, 62.3% [245/393] for 400 mg/day, and 63.4% [90/142] for 600 mg/day). The incidence of the most common drug-associated TEAEs was lower during the maintenance phase than during the titration phase for patients in the lacosamide group (Table 3).

3.6. Serious TEAEs during treatment

One death was reported in the double-blind trials. This male patient, who was randomized to lacosamide 200 mg/day, reported depression (due to spouse's illness), which was recorded as a nonserious TEAE (rated severe) 3 weeks prior to death (suicide) and was not considered by the investigator to be related to the trial medication. The incidence of other SAEs was higher among all patients who received lacosamide (6.5%) than placebo (3.8%). No overall dose effect was observed across the lacosamide treatment groups for SAEs (7.8% for 200 mg/day, 7.2% for 400 mg/day, and 3.0% for 600 mg/day). The most frequently reported SAEs (≥1% of patients in any lacosamide treatment group) were convulsion, dizziness, and nystagmus. Cases of convulsion that met criteria for SAEs were reported by 0.8% of patients who received lacosamide (*vs* 0.8% placebo), with a similar incidence across lacosamide doses (1.1% for 200 mg/day, 1.1% for 400 mg/day, and 0% for 600 mg/day). Cases of dizziness and nystagmus that were identified as SAEs occurred only in the lacosamide 600 mg/day group (1.5% for dizziness and 1.0% for nystagmus).

3.7. TEAEs leading to discontinuation

During the treatment phase, TEAEs led to discontinuation in 17.1% of patients in the lacosamide group (8.1%, 17.2%, and 28.6% for lacosamide 200, 400, and 600 mg/day groups, respectively; Table 4) and in 4.9% of

Table 3
Incidence of common drug-associated TEAEs[a] separated into the titration and maintenance phases in double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures (safety set).

MedDRA preferred term	Titration phase					Maintenance phase				
	Placebo (n = 364)	Adjunctive lacosamide (mg/day)				Placebo (n = 364)	Adjunctive lacosamide (mg/day)			
		200 (n = 270)	400 (n = 471)	600 (n = 203)	All doses (n = 944)		200 (n = 270)	400 (n = 471)	600 (n = 203)	All doses (n = 944)
Dizziness	24 (6.6)	28 (10.4)	116 (24.6)	96 (47.3)	240 (25.4)	6 (1.8)	18 (7.3)	33 (8.4)	14 (9.9)	65 (8.3)
Nausea	13 (3.6)	15 (5.6)	40 (8.5)	33 (16.3)	88 (9.3)	4 (1.2)	5 (2.0)	17 (4.3)	4 (2.8)	26 (3.3)
Diplopia	4 (1.1)	12 (4.4)	39 (8.3)	30 (14.8)	81 (8.6)	3 (0.9)	9 (3.7)	14 (3.6)	3 (2.1)	26 (3.3)
Vomiting	7 (1.9)	13 (4.8)	29 (6.2)	30 (14.8)	72 (7.6)	3 (0.9)	10 (4.1)	16 (4.1)	5 (3.5)	31 (4.0)
Fatigue	19 (5.2)	18 (6.7)	32 (6.8)	23 (11.3)	73 (7.7)	2 (0.6)	3 (1.2)	5 (1.3)	7 (4.9)	15 (1.9)
Vision blurred	6 (1.6)	5 (1.9)	29 (6.2)	30 (14.8)	64 (6.8)	3 (0.9)	3 (1.2)	12 (3.1)	4 (2.8)	19 (2.4)
Ataxia[b]	5 (1.4)	6 (2.2)	28 (5.9)	28 (13.8)	62 (6.6)	1 (0.3)	6 (2.4)	7 (1.8)	8 (5.6)	21 (2.7)
Tremor	12 (3.3)	4 (1.5)	20 (4.2)	22 (10.8)	46 (4.9)	3 (0.9)	6 (2.4)	9 (2.3)	2 (1.4)	17 (2.2)
Nystagmus	11 (3.0)	4 (1.5)	19 (4.0)	16 (7.9)	39 (4.1)	3 (0.9)	2 (0.8)	2 (0.5)	5 (3.5)	9 (1.2)
Balance disorder	0 (0)	2 (0.7)	17 (3.6)	8 (3.9)	27 (2.9)	0 (0)	2 (0.8)	8 (2.0)	5 (3.5)	15 (1.9)
Memory impairment	5 (1.4)	2 (0.7)	6 (1.3)	7 (3.4)	15 (1.6)	1 (0.3)	1 (0.4)	1 (0.3)	5 (3.5)	7 (0.9)

MedDRA, Medical Dictionary for Regulatory Activities.
For each TEAE, data are presented as n (%) of patients experiencing the TEAE at least once during the respective phase, based on the number of subjects with at least one dose administered during that phase.
[a] Common drug-associated TEAEs defined as those TEAEs occurring in ≥5% of patients in any lacosamide treatment group during the treatment phase and at least twice as often as in the placebo group.
[b] Coordination abnormal.

Table 4
Incidence of TEAEs leading to discontinuation[a] during the treatment phase (titration and maintenance) in double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures (safety set).

MedDRA preferred term	Placebo (n = 364)	Adjunctive lacosamide			
		200 mg/day (n = 270)	400 mg/day (n = 471)	600 mg/day (n = 203)	All doses of lacosamide (n = 944)
Any event	18 (4.9)	22 (8.1)	81 (17.2)	58 (28.6)	161 (17.1)
Dizziness	2 (0.5)	1 (0.4)	20 (4.2)	35 (17.2)	56 (5.9)
Ataxia[b]	0 (0)	1 (0.4)	6 (1.3)	11 (5.4)	18 (1.9)
Vomiting	1 (0.3)	1 (0.4)	11 (2.3)	6 (3.0)	18 (1.9)
Diplopia	1 (0.3)	4 (1.5)	10 (2.1)	4 (2.0)	18 (1.9)
Nausea	1 (0.3)	1 (0.4)	8 (1.7)	8 (3.9)	17 (1.8)
Vertigo	0 (0)	3 (1.1)	4 (0.8)	5 (2.5)	12 (1.3)
Vision blurred	0 (0)	1 (0.4)	3 (0.6)	6 (3.0)	10 (1.1)
Tremor	0 (0)	0 (0)	3 (0.6)	5 (2.5)	8 (0.8)
Nystagmus	0 (0)	0 (0)	1 (0.2)	5 (2.5)	6 (0.6)

MedDRA, Medical Dictionary for Regulatory Activities.
For each TEAE, data are presented as n (%) of patients discontinuing because of the TEAE.
[a] Data presented for TEAEs leading to discontinuation of ≥2% of patients in any lacosamide dose group.
[b] Coordination abnormal.

those on placebo. Dizziness and ataxia (coordination abnormal) were the only two TEAEs that individually led to >5% of patients discontinuing from any lacosamide dose group. Discontinuations due to dizziness increased with increasing lacosamide dose (0.4%, 4.2%, and 17.2% for lacosamide 200, 400, and 600 mg/day, respectively, *vs* 0.5% for placebo).

Discontinuations due to TEAEs according to the presence of each of the most commonly used AEDs as one of the concomitant AEDs in the combination therapy were: carbamazepine (15.3% [51/334] for lacosamide pooled doses *vs* 3.9% [5/129] for placebo), lamotrigine (19.2% [56/291] *vs* 4.3% [5/117]), levetiracetam (10.1% [28/278] *vs* 3.9% [4/103]), valproate (15.5% [33/213] *vs* 1.1% [1/95]), and topiramate (11.5% [24/208] *vs* 3.6% [3/83]) (note: 84.4% of patients took lacosamide in combination with more than one other AED; discontinuations reported here are not mutually exclusive for each AED).

SAEs led to discontinuation during the treatment phase by 2.9% of patients receiving lacosamide and 0.8% of those receiving placebo. The SAEs that most commonly led to discontinuation in lacosamide-treated patients were dizziness (0.3%) and convulsion (0.3%).

3.8. Other TEAEs of interest

Based on safety data from the double-blind trials and safety considerations for AEDs in general, additional TEAEs were identified *a priori* for evaluation. These TEAEs are of particular relevance to patients with POS taking AEDs.

3.8.1. Rash

The incidence of rash was similar for patients in the lacosamide group (n = 27, 2.9%) and those receiving placebo (n = 11, 3.0%), and was consistent across lacosamide dose groups (n = 4 [1.5%] for 200 mg/day, n = 16 [3.4%] for 400 mg/day, n = 34 [3.4%] for 600 mg/day). Incidence of rash was similar in the titration phase (2.0% of patients in the lacosamide group and 1.6% of the placebo group) and maintenance phase (1.2% of lacosamide patients and 1.5% of placebo patients). In addition, one patient experienced rash pruritic (lacosamide 600 mg/day) during the titration phase, and one patient experienced rash generalized (lacosamide 400 mg/day) during the maintenance phase; rash maculopapular was experienced by one patient in the placebo group. None of these rash events was considered serious, and no TEAE of Stevens–Johnson Syndrome or toxic epidermal necrolysis was reported. Among the 41 patients reporting a rash-related TEAE, the TEAE was considered by the investigator to be related to trial medication in eight (0.8%) lacosamide patients and in six (1.6%) placebo patients. Rash led to premature discontinuation from the trial by two (0.2%) lacosamide-treated patients and two (0.5%) placebo patients.

3.8.2. Select psychiatric events

Three patients who received lacosamide (0.3%) experienced a TEAE related to psychosis: one epileptic psychosis and two psychotic disorders. All three patients received lacosamide 400 mg/day, and all three TEAEs were considered serious. One of the cases of psychotic disorder was considered related to trial medication and led to discontinuation. No TEAE was related to psychosis in the placebo group.

The incidence of irritability was 1.5% in patients in the lacosamide group and 1.1% of placebo patients which is well below the threshold for reporting here but is of general interest.

Six patients randomized to lacosamide experienced events rated as suicidality-related in this population. Among these six cases, four (4/944; 0.4%) were reported to be receiving lacosamide at the time of the event, and two were not receiving the study drug at the time of event onset. One of the six patients represented a completed suicide (described in Section 3.6), while the remaining five patients were rated as suicidal ideation. No TEAE was related to suicidality in the placebo group.

Depression was reported by 20 (2.1%) patients randomized to lacosamide (six [2.2%] in the 200 mg/day group, 11 [2.3%] in the 400 mg/day group, three [1.5%] in the 600 mg/day group) and by two patients (0.5%) receiving placebo.

3.8.3. Seizure-related TEAEs

Seizure-related TEAEs were reported by 46 (4.9%) patients who received lacosamide and by 19 (5.2%) who received placebo. The most common seizure-related TEAE was convulsion, which was reported with a similar incidence for lacosamide (3.9%) and placebo (3.6%). Serious seizure-related TEAEs were reported by 13 (1.4%) patients who received lacosamide and by seven (1.9%) who received placebo. The most common serious seizure-related TEAE was convulsion, which occurred with a similar incidence in the lacosamide and placebo groups (0.8% for both). One SAE of status epilepticus was reported in the lacosamide 400 mg/day group, which resulted in the patient's discontinuation from the trial. There were a few discontinuations due to a seizure-related TEAE (12 [1.3%] patients who received lacosamide and six [1.7%] who received placebo); the seizure-related TEAE most frequently leading to discontinuation from the trial was convulsion (10 [1.1%] patients who received lacosamide and four [1.1%] who received placebo).

3.8.4. Body weight

A TEAE of weight increase was reported by 11 (1.2%) patients randomized to lacosamide (two patients in the 200 mg/day group, seven in the 400 mg/day group, two in the 600 mg/day group) and two (0.5%) in the placebo group. One patient in the lacosamide 400 mg/day group discontinued because of a TEAE of weight increase. Ten (1.1%) lacosamide-treated patients (two patients in the 200 mg/day group, four in the 400 mg/day group, and four in the 600 mg/day group) reported a TEAE of weight decrease, compared with three (0.8%) in the placebo group. One patient in the lacosamide 200 mg/day group discontinued because of a TEAE of weight decrease. No patient reported a SAE of increase or decrease in weight.

Mean (SD) changes in body weight during the treatment phase, measured as part of the vital signs assessment, were similar across lacosamide dose groups (+0.2 (2.7) kg for 200 mg/day, 0.0 (2.9) kg for 400 mg/day, +0.2 (3.6) kg for 600 mg/day *vs* +0.3 (2.6) kg for placebo). The proportion of patients exhibiting a ≥10% increase in body weight was similar between lacosamide (1.1%) and placebo (1.4%) groups, and was similar across lacosamide doses groups (1.5% for 200 mg/day, 0.6% for 400 mg/day, 1.0% for 600 mg/day). A decrease in body weight of ≥10% during the treatment phase was experienced by

1.5% of patients who received lacosamide and 1.4% of placebo patients, and was also similar across lacosamide dose groups (1.5% for 200 mg/day, 1.5% for 400 mg/day, 2.0% for 600 mg/day).

3.8.5. Post hoc analysis of TEAEs potentially related to cognition

The overall incidence of TEAEs identified as potentially related to cognition (see Section 2.4) was 7.7% for lacosamide and 4.7% for placebo (odds ratio [OR] 1.6, 95% confidence interval [CI] 0.9–2.8). The odds of reporting any potential cognition-related TEAE *vs* placebo increased with dose: 200 mg/day (incidence 1.9%) OR 0.4, 95% CI 0.1–1.2; 400 mg/day (incidence 8.5%) OR 1.7, 95% CI 1.0–3.1; 600 mg/day (incidence 13.8%) OR 2.8, 95% CI 1.3–5.7. Within the approved dose range (200 mg/day and 400 mg/day dose groups combined), the incidence of these cognition-related TEAEs was 6.1%, and was similar to placebo (OR 1.3, 95% CI 0.7–2.4). All individual TEAEs potentially related to cognition occurred with an incidence of <2% in the 200 mg/day and 400 mg/day groups, with the exception of cognitive disorder, which was reported by 2.1% of patients in the 400 mg/day group (Table 5).

3.9. Clinical chemistry values and vital signs

Abnormal clinical chemistry values reported as TEAEs that occurred with the highest incidence during the treatment phase were hypercholesterolemia (1.1% lacosamide *vs* 0.3% placebo), hyponatremia (0.6% lacosamide *vs* 0.3% placebo), increased gamma-glutamyl transferase (0.8% lacosamide *vs* 0.3% placebo) and increased blood triglycerides (0.6% lacosamide *vs* 0.5% placebo). Treatment-emergent elevations of alanine aminotransferase to ≥3 times the upper limit of normal occurred in 0.5% of lacosamide-treated patients and in 0% of placebo patients. No patient in any treatment group had a maximum total bilirubin value ≥2 times the upper limit of normal. The TEAE of liver function test abnormal was reported by three lacosamide patients (0.3%).

Six lacosamide-treated patients discontinued the study because of TEAEs related to abnormal clinical chemistry values. One patient (200 mg/day) withdrew from the study because of liver function test abnormality, three because of elevated liver enzymes (two on 200 mg/day, one on 400 mg/day), and two because of hyponatremia (one each on 400 mg/day and 600 mg/day). No discontinuations due to abnormal clinical chemistry values were reported in the placebo group.

All mean/median values for hematology parameters for patients receiving lacosamide remained within the normal range and were not different from the placebo group. There were no consistent trends or changes from baseline for any hematology parameters considered to be related to lacosamide treatment.

Mean changes in blood pressure and pulse rate were minimal across all lacosamide treatment groups and were similar to the placebo group. Similarly, no clinically relevant changes for any additional vital sign parameters considered likely to be related to lacosamide treatment were observed.

3.10. Cardiac events

The placebo-adjusted mean maximum increase in PR interval with lacosamide was 1.5 ms for 200 mg/day, 3.1 ms for 400 mg/day, and 4.5 ms for 600 mg/day. Four lacosamide-treated patients had a nonserious TEAE of first degree atrioventricular (AV) block (two patients receiving 200 mg/day, one receiving 400 mg/day, and one receiving 600 mg/day). No patient in the placebo group experienced first degree AV block. There were no findings of second degree or higher AV block.

4. Discussion

The analyses reported here were performed by pooling data from three pivotal double-blind, placebo-controlled trials of adjunctive lacosamide in adults with POS to determine whether any new safety trends or safety risks associated with lacosamide treatment could be detected in a larger patient population. Although the majority of the 1308 patients in this pooled dataset reported at least one TEAE, most TEAEs were mild or moderate in intensity. Furthermore, three-quarters of patients who were randomized and 96% of those who completed the double-blind trials were enrolled in the subsequent lacosamide open-label extensions, suggesting that most patients and physicians found the tolerability of lacosamide to be favorable. The most common drug-associated TEAEs were typically related to nervous and gastrointestinal systems and generally appeared to be dose-related. For all lacosamide doses combined, dizziness, nausea, and diplopia occurred with an incidence of ≥10%.

Among all patients who received lacosamide, no individual SAE occurred in ≥1% of patients; this is consistent with what was noted in each of the individual trials [10–12]. The most frequently reported SAEs (≥1% of patients in any lacosamide dose group) were convulsion, dizziness, and nystagmus. Dizziness and nystagmus were reported as SAEs only with the highest dose (600 mg/day), and convulsion generally occurred with a similar incidence for placebo and lacosamide.

A dose relationship was apparent for all of the common TEAEs considered to be associated with lacosamide in these pooled analyses, similar to most other AEDs. The most frequently reported TEAEs associated with adjunctive lacosamide treatment occurred with a notably lower incidence during the maintenance phase than during the titration phase. This may be due to how the data were recorded with onset occurring in the titration phase but continuing during the maintenance phase being only recorded as having onset in the titration phase. However, this result may also be related, at least in part, to the design of the trials, which employed forced titration to a predefined target dose and required concomitant AEDs to be maintained at a stable dose [10–12]. These pooled analyses align with a recent meta-analysis of randomized controlled trials of lacosamide in patients with POS, neuropathic pain, migraine, fibromyalgia, or knee osteoarthritis [25], and considered together, these data suggest that some patients may be most susceptible to AEs during dose adjustment. Flexible dosing of AEDs including lacosamide, as well as adjustment of existing AED regimens, is routinely

Table 5
TEAEs potentially related to cognition[a] during the treatment phase of double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures (safety set).

MedDRA preferred term	Placebo (n = 364)	Adjunctive lacosamide			
		200 mg/day (n = 270)	400 mg/day (n = 471)	600 mg/day (n = 203)	All doses of lacosamide (n = 944)
Memory impairment	6 (1.6)	3 (1.1)	7 (1.5)	12 (5.9)	22 (2.3)
Cognitive disorder	1 (0.3)	1 (0.4)	10 (2.1)	4 (2.0)	15 (1.6)
Confusional state	3 (0.8)	0 (0)	7 (1.5)	7 (3.4)	14 (1.5)
Disturbance in attention	2 (0.5)	0 (0)	5 (1.1)	4 (2.0)	9 (1.0)
Mental impairment	0 (0)	0 (0)	2 (0.4)	2 (1.0)	4 (0.4)

MedDRA, Medical Dictionary for Regulatory Activities.
For each TEAE, data are presented as n (%) of patients experiencing the TEAE at least once.
[a] Data presented for TEAEs potentially related to cognition with an incidence of ≥1% during the treatment phase in any lacosamide dose group.

practiced in the clinical setting, and this tailoring of dose to individual patient response differs from the fixed-dose allocation and stable background AEDs used in these clinical trials. Therefore, the higher incidence of TEAEs during AED titration in the present study may be better managed in clinical practice.

A dose-dependent increase in discontinuations due to TEAEs was observed, with dizziness reported as the most common cause. *Post hoc* analyses from these pivotal trials, as well as studies conducted in a real-life setting, suggest a potential for improved tolerability when lacosamide was added to an AED regimen that did not include sodium channel-blocking AEDs, especially at higher lacosamide dosages [23,26–28]. The *post hoc* analysis of TEAEs leading to discontinuation according to concomitant AED use reported here is difficult to interpret because the sample size for concomitant AED groups was unbalanced, concomitant AED groupings were not mutually exclusive, and the majority of patients (84%) were taking at least two concomitant AEDs. However, the trend of the findings suggests that nervous system TEAEs occurred more frequently for patients on concomitant sodium channel blockers.

Included in this detailed assessment of lacosamide safety was an evaluation of TEAEs that have been identified to be of particular interest in patients taking AEDs [29–32]. Similar to other AEDs, the use of adjunctive lacosamide treatment was associated with TEAEs related to the nervous system, and this was found predominantly during the titration phase. However, no trends in the nature or frequency of seizure-related TEAEs, or TEAEs of rash, psychiatric disturbances, weight change, or changes in clinical chemistry values or vital signs were found. Selected TEAEs potentially related to cognitive impairment were analyzed *post hoc*, and the incidence was similar between lacosamide dosages of 200 mg/day and 400 mg/day and placebo. These overall observations from selected TEAEs are generally consistent with a retrospective study assessing the impact of lacosamide and other AEDs (topiramate and lamotrigine) on cognition using EpiTrack® in patients with epilepsy [33]. This naturalistic study indicated that the cognitive side effect profile of lacosamide was comparable to that of lamotrigine, whereas topiramate performed worse than both lacosamide and lamotrigine, as indicated by both subjective and objective measures [33]. With respect to cardiac events, a small, dose-related increase in PR interval was observed with adjunctive lacosamide treatment, but this did not lead to clinically significant delay in cardiac conduction. A full review of cardiac safety data in patients with POS has been conducted and published elsewhere [34]. Based on all available data, it is recommended that lacosamide should continue to be used with caution in patients with known conduction problems or sodium channelopathies, patients on drugs known to induce PR interval prolongation, or those with severe cardiac disease such as myocardial ischemia, heart failure, or structural heart disease; the US but not the EU label recommends that in such patients, an ECG should be obtained before beginning lacosamide, and after lacosamide is titrated to steady-state, maintenance dose is recommended [1,2].

Overall, *a priori* and *post hoc* safety analyses provide a more detailed description of the lacosamide safety profile across the dose range of 200–600 mg/day in adults with epilepsy and uncontrolled POS, most of whom were taking 2–3 concomitant AEDs. The results of these analyses confirm and extend earlier findings from the individual trials that lacosamide was generally well tolerated, with the best tolerability observed for the approved dose range (200–400 mg/day).

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Conflicts of interest and sources of funding

Individual trials as well as pooled analyses were funded by UCB Biosciences Inc., Raleigh, NC, USA. Dr. Biton is currently an investigator for Eisai, Elan/Janssen, King, Medivation, Pfizer, Sepracor/Sunovion, UCB Pharma, Xenoport, Lundbeck, Schering-Plough/Merck, Upsher-Smith, SK Life Sciences, and Wyeth. Dr. Biton has recently been an investigator for Marinus, Schwarz (a member of the UCB group), Johnson & Johnson, Vernalis, Valeant, Forest, Genzyme, Icagen, Supernus, Vertex, and Myriad. Dr. Gil-Nagel has received research grants from UCB Pharma and Eisai, has received consulting fees from Bial, Eisai, Medtronic, GSK, UCB Pharma, and Valeant, and has received speaker's honorarium from GSK, Medtronic, Eisai, Bial, and UCB Pharma. Dr. Isojarvi was an employee of UCB Biosciences Inc. from January 2008 to November 2011 and has received stock/stock options from UCB. Drs. Doty and Hebert are employees of UCB Biosciences Inc. Dr. Fountain has received research grants from UCB Pharma, Lundbeck, SK Life Sciences, Medtronic, NeuroPace, and NIH, and has received travel reimbursement and consulting fees from UCB Pharma.

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