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FULL-LENGTH ORIGINAL RESEARCH

Safety and tolerability of adjunctive lacosamide intravenous loading dose in lacosamide-naive patients with partial-onset seizures

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Summary

Purpose: To examine the safety and tolerability of rapidly initiating adjunctive lacosamide via a single intravenous loading dose followed by twice-daily oral lacosamide in lacosamide-naive adults with partial-onset seizures.

Methods: This open-label, multicenter trial, enrolled patients with epilepsy who were taking 1–2 antiepileptic drugs (AEDs) in one of four sequential cohorts containing 25 subjects each. An intravenous lacosamide loading dose (200, 300, or 400 mg) was administered over 15 min followed 12 h later by initiation of oral dosing consisting of one-half of the loading dose administered twice daily for 6.5 days. The first cohort was administered lacosamide 200 mg/day, followed by a cohort at 300 mg/day, and then a cohort at 400 mg/day. The results from each cohort were evaluated before enrolling the next highest dose level. The fourth cohort enrolled patients at the highest dose with clinically acceptable safety and tolerability results. Safety evaluations included treatment-emergent adverse events (TEAEs), patient withdrawals due to TEAEs, and changes in vital signs, 12-lead electrocardiography (ECG) studies, laboratory parameters, and clinical examinations. Postinfusion lacosamide plasma concentrations were also evaluated.

Key Findings: A total of 100 patients were enrolled, 25 in each cohort. The loading dose for the repeat cohort was 300 mg; therefore, 25 patients were enrolled at 200 mg/day, 50 at 300 mg/day, and 25 at 400 mg/day. Most TEAEs occurred within the first 4 h following infusion; dose-related TEAEs (incidence ≥10%) during this timeframe included dizziness, somnolence, and nausea. Seven patients withdrew, all due to TEAEs: three (6%) from the combined 300 mg group and four (16%) from the 400 mg group; four of these patients discontinued within 4 h following infusion. The most common TEAEs leading to discontinuation (overall incidence >1%) were dizziness (6%), nausea (5%), and vomiting (3%). No clinically relevant pattern of changes from baseline ECG, clinical laboratory parameters, or vital signs were observed. Trough plasma concentrations suggested that near steady-state lacosamide concentrations were achieved with a single intravenous loading dose.

Significance: Intravenous loading doses of 200 and 300 mg lacosamide administered over 15 min followed by oral lacosamide were well tolerated in lacosamide-naive patients. The 400-mg loading dose was less well tolerated due to a higher frequency of dose-related TEAEs. These results support the feasibility of rapid initiation of adjunctive lacosamide treatment.

KEY WORDS: Seizures, Lacosamide, Intravenous, Clinical trial.

When oral antiepileptic drug (AED) use is impossible or impractical, such as after surgery, during gastrointestinal illness, or for cases of dysphagia, the availability of a well-tolerated intravenous AED is a medical necessity. It is also useful in medical emergencies when AEDs must be given rapidly by the intravenous route (Wheless & Venkataraman, 1999). Lacosamide, a newer AED approved for the adjunctive treatment of partial-onset seizures (POS), is available as an oral tablet and oral solution, and as an intravenous formulation (Stephen & Brodie, 2011). The efficacy of oral lacosamide in patients with uncontrolled POS was established in three double-blind, placebo-controlled trials (SP667, SP754 [NCT00136019], and SP755 [NCT00220415]) (Ben-Menachem et al., 2007; Halasz et al., 2009; Chung et al., 2010). Studies of intravenous lacosamide in healthy volunteers showed that 60- and 30-min infusions were bioequivalent to oral lacosamide; however, bioequivalence criteria for the 15-min intravenous lacosamide infusions were met for area under the concentration-time curve (AUC) but not for maximum plasma concentration (C_{max}), which slightly

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exceeded the upper boundary of the bioequivalence range and raises the possibility that a higher C_{max} might reduce tolerability (Kropeit et al., 2004; Bialer et al., 2009). Therefore, tolerability of a specific dose of oral lacosamide could theoretically be different from the tolerability of that same dose administered as an intravenous infusion over 15 min.

Intravenous lacosamide 200–400 mg/day (given as two divided doses) infused over 60- and 30-min is approved as a short-term replacement for oral lacosamide in adult patients with POS. Safety data of intravenous lacosamide is available over the dose range of 200–800 mg/day and for infusion durations of 60-, 30-, 15-, and 10-min from patients already taking oral lacosamide (SP616 [NCT00800215] and SP757 [NCT00151879]) (Biton et al., 2008; Krauss et al., 2010). Few treatment emergent adverse events (TEAEs) were reported in these patients, likely because they were already receiving oral lacosamide. One serious adverse event (SAE) of bradycardia was reported, but review by external cardiologists suggested this was possibly a vasovagal episode (Krauss et al., 2010). The patient fully recovered, discontinued intravenous lacosamide study, and returned to the oral lacosamide open-label extension trial. With the exception of a few injection-site reactions (usually mild and self limited), the nature of TEAEs in these trials was comparable to that observed with oral lacosamide; however, the tolerability of rapid intravenous infusion in lacosamide-naive patients remained to be characterized.

The objective of this phase 3b, multicenter, open-label trial (SP925 [NCT00655551]) was to examine the safety and tolerability of rapid initiation of adjunctive lacosamide via a single 15-min intravenous loading dose (200, 300, or 400 mg) followed by twice-daily oral lacosamide maintenance treatment in lacosamide-naive adults with POS.

Methods

Patients

Eligible participants were lacosamide-naive, age 16–60 years (inclusive), diagnosed with simple partial and/or complex partial seizures with or without secondary generalization and maintained on a stable dose of 1–2 concomitant AEDs, with or without vagus nerve stimulation (VNS). Patients must have been experiencing one or more partial seizures with a motor component per 90 days (40 partial seizures maximum in 28 days prior to trial entry) and considered by the investigator as a patient who could benefit from adjunctive AED treatment. Key exclusion criteria were previous lacosamide use; history of primary generalized seizures; status epilepticus within the previous 12 months; current use of neuroleptics, monoamine oxidase inhibitors, barbiturates, or narcotic analgesics; more than one rescue use of benzodiazepines within 28 days before screening; alcohol or drug abuse in the last 2 years; medical or psychiatric conditions that could jeopardize the patient's health or compromise his/her ability to participate in the trial; diastolic blood pressure <50 or >105 mm Hg; heart rate <50 or >100 beats/min; heart failure; myocardial infarction within the last 12 months; clinically relevant abnormal ECG findings including arrhythmias; or creatinine clearance <50 ml/min. Female participants were excluded if pregnant, breastfeeding, or of childbearing potential and not using approved contraceptive methods.

Trial design

This open-label intravenous loading dose trial was conducted between April 2008 and September 2009 at eight sites in the United States in accordance with the current version of the applicable regulatory and International Conference on Harmonisation (ICH)–Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the United States. The trial protocol, amendments, and informed consents were reviewed by the applicable institutional review boards. All patients or their legal representatives provided written informed consent before trial participation. Seizure frequency was not analyzed as part of this study, since the efficacy of adjunctive lacosamide had already been established (Ben-Menachem et al., 2007; Halasz et al., 2009; Chung et al., 2010). Furthermore, the cyclical pattern of partial-onset seizure frequency coupled with the short duration of the study (7 days) would have precluded meaningful assessment of change in seizure frequency in this study.

Trial participants were enrolled into one of four sequential cohorts, each comprised of 25 unique patients (Fig. 1). A data monitoring committee (DMC) review was conducted following completion of a cohort to determine if it was acceptable to enroll patients into a subsequent cohort (either at the next higher dose or a previous dose). The first cohort was to receive a 200-mg intravenous loading dose followed by 100-mg oral lacosamide twice daily; the second cohort was to receive a 300-mg intravenous loading dose and 150 mg orally twice daily, and the third cohort was to receive a 400-mg intravenous loading dose and 200 mg orally twice daily. If reached, the final cohort was to repeat the loading dose that was determined to be the highest dose that produced clinically acceptable safety results.

Treatment schedule

Patients were administered intravenous lacosamide over 15 min on the morning of day 1. Intravenous lacosamide (10 mg/ml) was administered (undiluted) by infusion into an arm vein using approved standardized polyvinylchloride or polyethylene tubing and a calibrated syringe pump. Patients remained recumbent for 5 min before the predose ECG and vital signs measurements, during infusion, and for approximately 2 h following intravenous infusion. Oral lacosamide tablets were given under supervision the evening of day 1 as well as the morning of day 2. Before discharge, patients were instructed to continue oral dosing twice daily

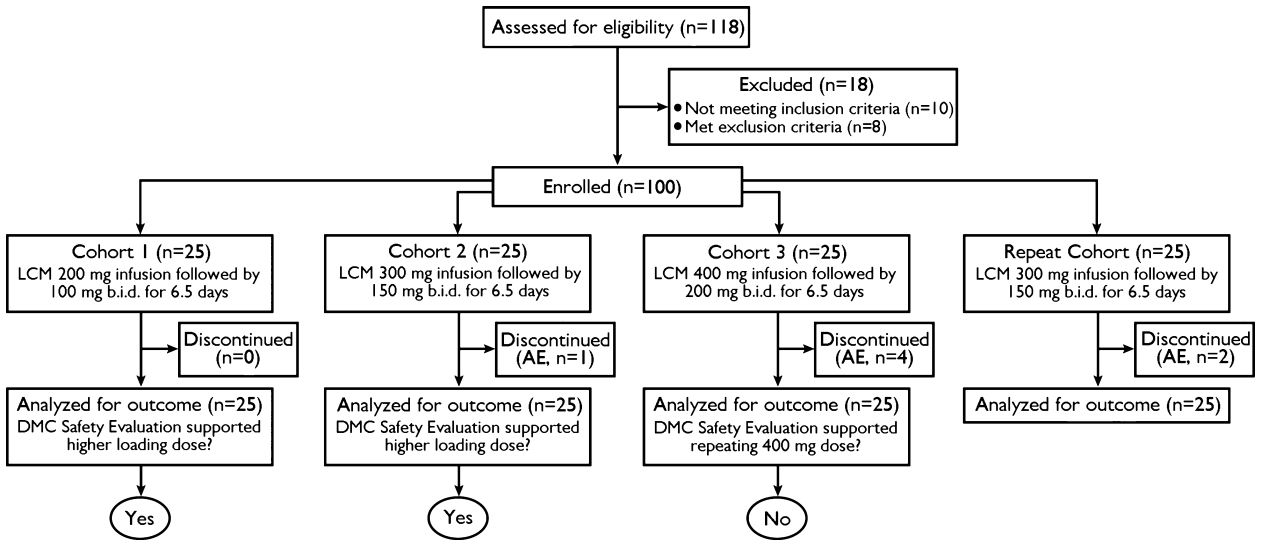

Figure 1.
Trial diagram.
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at 12-h intervals for the next 5.5 days (final dose on day 7 evening). Upon completion of the 7-day Treatment Period, patients returned for an End of Trial Visit (day 8 morning). Following completion of the trial, participants were given the opportunity to either enter an extension trial at the same lacosamide dose or have lacosamide tapered and discontinued.

Safety variables

The primary outcome variables were TEAEs reported spontaneously by the patient and/or caregiver or observed by the investigator, and patient withdrawals due to TEAEs. TEAEs were analyzed by the following time points: 0–4 h post-infusion start (defined by the DMC as "infusion related"), 4–12 h post infusion, and >12 h post infusion. Other safety variables included changes in 12-lead ECGs and vital sign measurements acquired midinfusion, at the end of infusion, prior to oral dose administration 12- and 24-h after infusion, and at trial end. Changes in hematology, chemistry, and urinalysis parameters as well as physical and neurologic examinations were evaluated at trial end.

Pharmacokinetic assessment

Blood samples for the determination of lacosamide plasma concentrations were drawn at the end of loading dose infusion, just before the next two oral doses (trough values) and on the last day of the trial. Postinfusion blood samples were drawn from the arm opposite intravenous infusion. Samples were centrifuged; plasma was harvested and split into two duplicate samples and stored at −20°C until shipped to a central laboratory for analyses using validated high-performance liquid chromatography (HPLC) methods.

Statistical analysis

Statistical analyses were performed using SAS Version 9.1.3 (SAS Institute, Cary, NC, U.S.A.). Descriptive statistics were used to provide an overview of the trial results. For categorical parameters, descriptive statistics consisted of the number and percentage of patients in each category. For continuous parameters, descriptive statistics included n (number of patients), mean, standard deviation (SD), median, minimum, and maximum. No power analysis was done because the study was exploratory and it is anticipated that the frequency of adverse events would be too low for statistical hypothesis testing. Important TEAEs were anticipated to occur at a low rate, and the statistical differences between groups would not be detected due to the limited number of patients enrolled.

Two analysis populations were defined for this trial: the Safety Set (SS) was comprised of all patients who were given one dose or more of trial medication (for analysis for safety parameters), and the Pharmacokinetic Set (PKS), which included a subset of patients in the SS with valid plasma concentration data.

TEAEs were defined as those events that started or whose severity worsened on or after the date of the first dose of trial medication. Adverse events with onset or worsening intensity up to 30 days after the day of last dose of trial medication were considered treatment-emergent.

Summaries of TEAEs are presented by the assigned dose groups. During the trial, two patients in the combined 300 mg group received 400 mg intravenous lacosamide infusions. Therefore, ensuing patient tolerability data were also analyzed by the dose actually received to reflect the tolerability associated with the intravenous lacosamide dose.

Summary statistics of actual values and their change from Baseline (defined as visit 1) were examined for continuous laboratory, vital sign, and ECG variables.

Results

Patient disposition

Ninety-three of the 100 enrolled patients in the SS completed the 7-day trial; seven patients discontinued prematurely due to TEAEs (three in the combined 300 mg group and four in the 400 mg group). Per the protocol, patients who completed the trial or discontinued due to lack of tolerability (300 and 400 mg/day groups) were allowed to participate in an open-label extension trial (SP926 [NCT00655486]). Overall, 97 patients (97%) entered SP926; of the three patients who opted not to continue, two completed trial SP925 and one discontinued due to an AE.

Demographics

Baseline demographics and characteristics were similar across all lacosamide dose groups (Table 1). Most patients (69%) were treated with two concomitant AEDs; the most common concomitant AEDs included levetiracetam, lamotrigine, and oxcarbazepine (Table 2). There were 75 patients taking sodium channel blocking AEDs and 25 not taking sodium channel blocking AEDs. The incidence of adverse events was too small to provide meaningful comparisons between these groups.

Lacosamide exposure

During the trial, mean lacosamide exposure was 7.6 days. All but three patients received the correct intravenous lacosamide infusion dose: two patients in the combined 300-mg group incorrectly received 400-mg lacosamide infusion and one patient in the 200 mg group did not receive the full dose due to an error related to loading the empty air space in the intravenous tubing.

Safety data

Overall TEAEs and intensities

A total of 79 patients (79%) reported at least 1 TEAE (Table 3). Most TEAEs appeared to be dose-related and were mild or moderate in intensity. The most common TEAEs (incidence ≥10% in any dosing group) were dizziness, somnolence, nausea, fatigue, diplopia, headache, dry mouth, vision blurred, vomiting, and chest pain. Of these, diplopia, dizziness, dry mouth, nausea, vision blurred, and

Table 1. Baseline demographics and characteristics (safety set[a])

	LCM 200 mg n = 25	Combined LCM 300 mg[b] n = 50	LCM 400 mg n = 25	Overall N = 100
Age, mean (SD), years	39.1 (11.77)	38.6 (11.53)	39.6 (12.24)	39.0 (11.66)
Gender, no. (%)				
Male	11 (44)	24 (48)	16 (64)	51 (51)
Female	14 (56)	26 (52)	9 (36)	49 (49)
Weight, mean (SD), kg	81.0 (27.63)	85.0 (19.44)	87.5 (22.57)	84.6 (22.38)
BMI, mean (SD), kg/m^2	27.6 (7.29)	29.6 (7.52)	29.2 (7.41)	29.0 (7.41)
Race, no. (%)				
White	18 (72)	42 (84)	23 (92)	83 (83)
Black	5 (20)	7 (14)	1 (4)	13 (13)
Asian	1 (4)	0	0	1 (1)
Other	1 (4)	1 (2)	1 (4)	3 (3)
Time since diagnosis, mean (SD), years	20.0 (12.16)	23.0 (13.54)	26.8 (16.08)	23.2 (13.97)
Lifetime AEDs, no. (%)				
1–3	8 (32)	20 (40)	9 (36)	37 (37)
4–6	7 (28)	15 (30)	5 (20)	27 (27)
≥7	9 (36)	15 (30)	11 (44)	35 (35)
Unknown	1 (4)	0	0	1 (1)
Concomitant AEDs, no. (%)				
1	5 (20)	17 (34)	9 (36)	31 (31)
2	20 (80)	33 (66)	16 (64)	69 (69)
VNS use, no. (%)				
Yes	3 (12)	8 (16)	7 (28)	18 (18)
No	9 (36)	11 (22)	5 (20)	25 (25)
NA	13 (52)	31 (62)	13 (52)	57 (57)

[a]Safety Set = two patients in the repeat 300-mg cohort who received an infusion of 400-mg lacosamide were analyzed with assigned 300-mg cohort.
[b]Combined cohort = cohort 2 and repeat cohort (300-mg lacosamide).
LCM, lacosamide; VNS, vagus nerve stimulation.
VNS categories are defined as follows: Yes = VNS active, No = VNS not active, NA (not applicable) = never used VNS.

Table 2. Summary of concomitant AEDs by dose group (≥10% overall; safety set[a], as assigned)

AED	LCM 200 mg n = 25 no. (%)	Combined LCM 300 mg[b] n = 50 no. (%)	LCM 400 mg n = 25 no. (%)	Overall N = 100 no. (%)
Levetiracetam	11 (44)	20 (40)	4 (16)	35 (35)
Lamotrigine	12 (48)	9 (18)	8 (32)	29 (29)
Oxcarbazepine	6 (24)	11 (22)	3 (12)	20 (20)
Topiramate	7 (28)	5 (10)	7 (28)	19 (19)
Carbamazepine	4 (16)	10 (20)	4 (16)	18 (18)
Phenytoin	0	7 (14)	5 (20)	12 (12)
Zonisamide	1 (4)	8 (16)	3 (12)	12 (12)

[a]Safety Set = two patients in the repeat 300-mg cohort who received an infusion of 400-mg lacosamide were analyzed with assigned 300-mg cohort.
[b]Combined cohort = cohort 2 and repeat cohort (300-mg lacosamide).
LCM, lacosamide.

Table 3. Summary of treatment emergent adverse events overall and within 4 h of start of infusion (incidence ≥10% in any dosing group; safety set[a], as assigned)

Preferred term	LCM 200 mg n = 25	Combined LCM 300 mg[b] n = 50	LCM 400 mg n = 25	Overall N = 100
TEAEs overall, no. (%)				
Dizziness	5 (20)	23 (46)	15 (60)	43 (43)
Somnolence	0	17 (34)	9 (36)	26 (26)
Nausea	0	8 (16)	6 (24)	14 (14)
Fatigue	0	9 (18)	3 (12)	12 (12)
Diplopia	1 (4)	3 (6)	5 (20)	9 (9)
Headache	2 (8)	2 (4)	4 (16)	8 (8)
Dry mouth	0	3 (6)	3 (12)	6 (6)
Vision blurred	0	2 (4)	3 (12)	5 (5)
Vomiting	0	2 (4)	3 (12)	5 (5)
Chest pain	0	0	3 (12)	3 (3)
TEAEs onset within 4 h of start of infusion, no. (%)				
Dizziness	1 (4)	10 (20)	10 (40)	21 (21)
Somnolence	0	10 (20)	5 (20)	15 (15)
Nausea	0	2 (4)	5 (20)	7 (7)
Diplopia	1 (4)	0	3 (12)	4 (4)

[a]Safety Set = two patients in the repeat 300-mg cohort who received an infusion of 400-mg lacosamide were analyzed with assigned 300-mg cohort.
[b]Combined cohort = cohort 2 and repeat cohort (300-mg lacosamide).
LCM, lacosamide.

vomiting appeared to be dose-related. One patient (400 mg group) reported injection site swelling.

TEAEs by time point

Onset within 4 h following start of infusion. A total of 45 patients experienced at least 1 TEAE within 4 h of Start of Infusion (Table 3). During this timeframe, the most common TEAEs (incidence ≥10% in any dose group) were dizziness, somnolence, nausea, and diplopia. Of these, only diplopia did not appear to be dose related. One patient in the 400-mg group reported severe diplopia following the intravenous loading dose and recovered before the oral lacosamide dose, but withdrew from the trial the following day due to dizziness, hyperhidrosis, and nausea.

Onset between 4 and 12 h following start of infusion. Ten patients experienced TEAEs with onset between 4 and 12 h after Start of Infusion (prior to oral lacosamide dosing). The overall incidence of TEAEs was <5% for all events reported in this interval and included headache (3%), diarrhea (2%), hot flush (2%), nausea (2%), fatigue (1%), injection site swelling (1%), and pain in extremity (1%). All events were mild or moderate in intensity.

TEAE analysis by actual intravenous dose received

The analyses of TEAEs overall and 0–4 h post-infusion were repeated with the two patients in the 300-mg group, who received a higher infusion dose, analyzed with the 400-mg group. The most common TEAEs reported for each group were the same as originally reported except for the additional TEAE of hypoesthesia oral in the 400-mg group.

Incidence of serious TEAEs

The one SAE reported in the trial (chest pain) occurred in a patient in the 400-mg group on day 8 (one day after taking the last oral lacosamide dose) and lasted 2 days. The event was of moderate intensity and was judged by the investigator not to be cardiac-related but rather anxiety-related, and unrelated to lacosamide treatment; the patient continued into trial SP926.

Discontinuations

Seven patients discontinued the trial prematurely due to TEAEs; four of these patients reported TEAEs leading to discontinuation within 4 h following Start of Infusion. Generally, the types of TEAEs leading to discontinuation were similar regardless of the time of onset and were consistent with the most frequently reported TEAEs for the overall trial population. TEAEs that led to discontinuation of more than one patient were dizziness, nausea, and vomiting (Table 4). The majority of these TEAEs were mild or moderate in intensity; severe TEAEs leading to discontinuation were reported by two patients (dizziness in one patient; asthenia, dizziness, and nausea in one patient). All of the TEAEs leading to discontinuation were considered by the investigator to be related to lacosamide; none were serious and all resolved.

Changes in laboratory, ECG, and vital sign values

No clinically relevant postbaseline trends in clinical laboratory data or physical and neurologic examinations were observed during the trial. Assessment of ECG results measured at the end of infusion showed an increase from

Table 4. Treatment emergent adverse events leading to discontinuation (safety set[a])

Preferred term	LCM 200 mg n = 25 no. (%)	Combined LCM 300 mg[b] n = 50 no. (%)	LCM 400 mg n = 25 no. (%)	Overall N = 100 no. (%)
Any event	0	3 (6)	4 (16)	7 (7)
Dizziness	0	3 (6)	3 (12)	6 (6)
Nausea	0	2 (4)	3 (12)	5 (5)
Vomiting	0	1 (2)	2 (8)	3 (3)
Asthenia	0	1 (2)	0	1 (1)
Coordination abnormal	0	1 (2)	0	1 (1)
Fatigue	0	1 (2)	0	1 (1)
Gait disturbance	0	1 (2)	0	1 (1)
Sedation	0	1 (2)	0	1 (1)
Headache	0	0	1 (4)	1 (1)
Hyperhidrosis	0	0	1 (4)	1 (1)

[a]Safety Set = two patients in the repeat 300-mg cohort who received an infusion of 400-mg lacosamide were analyzed with assigned 300-mg cohort.
[b]Combined cohort = cohort 2 and repeat cohort (300-mg lacosamide).
LCM, lacosamide.

baseline in mean PR interval (6.1 msec for the 200-mg group; 8.6 msec for the combined 300-mg group; 10.6 msec for the 400-mg group), and a mean change from baseline for QRS duration of −1.3, 0.7, and 2.9 msec for the same dose groups, respectively. There was no tendency for prolongation of the QTc Fridericia interval. There were no clinically relevant mean changes in blood pressure or heart rate across groups.

Pharmacokinetic analysis

The mean plasma concentrations of lacosamide at the end of infusion across dose groups were dose proportional (Table 5). The means for C_{trough} on day 1 (prior to the first oral dose) and on day 2 (before the dose the next morning) were less than the peak plasma concentration achieved immediately after infusion. C_{trough} on day 2 was slightly higher than day 1, but the means between day 1 and day 2 were similar.

Discussion

This trial is the first to examine rapid lacosamide loading in lacosamide-naive patients with uncontrolled POS. All 100 patients enrolled in the trial completed intravenous lacosamide infusion, suggesting the feasibility of rapid initiation of adjunctive lacosamide via intravenous infusion. DMC safety data evaluation concluded that loading doses of intravenous lacosamide 200 and 300 mg administered over 15 min were tolerated best, and the 300-mg dose was selected as the infusion dose for the repeat cohort, yielding 50 patients in this dose group. The 400-mg loading infusion was less well tolerated due to a higher frequency of dose-related adverse events.

Most TEAEs occurred within 4 h of the start of lacosamide infusion and are reasonably attributed to the infusion, either from the rapidity of infusion or the dose. The most commonly reported TEAEs were typical for neuroactive drugs and AEDs in particular. In the 4–12 h interval, the overall incidence of TEAEs was <5% for all events, suggesting that the events occurring early were related to infusion and were time limited. Over the 6.5-day oral lacosamide treatment period, only dizziness and diplopia occurred at an incidence ≥10% in any dosing group. Although the TEAEs reported during this trial were consistent in nature with those reported in the double-blind, placebo-controlled trials, the incidences of TEAEs were higher than those observed in the trials where intravenous lacosamide was administered as a replacement to oral therapy in patients with POS (SP616 and SP757). This difference is likely due to the inclusion of lacosamide-naive patients who received intravenous lacosamide without titration, whereas patients in previous intravenous trials were titrated to and maintained on a stable dose of oral lacosamide prior to intravenous replacement treatment.

Seven patients discontinued the trial prematurely due to TEAEs, with four of these discontinuations occurring within 4 h of Start of Infusion. In general, the types of TEAEs leading to discontinuation were similar regardless of the time of

Table 5. Summary of lacosamide plasma concentrations by dose group (pharmacokinetic set[a])

Assessment time	Statistics	LCM 200 mg n = 25	Combined LCM 300 mg[b] n = 50	LCM 400 mg n = 25
Day 1/End of infusion	n	23	45	23
	Mean (SD) (μg/ml)	6.586 (2.218)	9.319 (3.765)	12.330 (4.118)
	Min, Max (μg/ml)	3.193, 12.130	0.683, 16.017	4.779, 23.133
Day 1/Evening predose	n	23	40	19
	Mean (SD) (μg/ml)	2.927 (1.276)	3.243 (1.162)	4.500 (1.625)
	Min, Max (μg/ml)	1.612, 7.674	1.108, 8.154	2.843, 8.794
Day 2/Morning predose	n	20	45	21
	Mean (SD) (μg/ml)	3.379 (1.694)	3.844 (1.730)	4.917 (1.499)
	Min, Max (μg/ml)	1.794, 9.091	1.610, 11.067	3.384, 9.026

[a]Pharmacokinetic set = two patients in the repeat 300-mg cohort who received an infusion of 400-mg lacosamide were analyzed with assigned cohort.
[b]Combined cohort = cohort 2 and repeat cohort (300-mg LCM).

onset and were consistent with the most frequently reported TEAEs for the whole trial population, which probably reflects the known tolerability of lacosamide from oral dosing studies.

Evaluation of changes in laboratory, ECG, and vital sign values following intravenous loading and oral maintenance treatment with lacosamide were consistent with the known lacosamide oral and intravenous safety profile (Ben-Menachem et al., 2007; Biton et al., 2008; Halasz et al., 2009; Chung et al., 2010; Krauss et al., 2010) and did not raise any particular concerns for the 15-min infusion duration.

Administration of a single intravenous lacosamide loading dose at two times the oral maintenance dose achieved peak lacosamide C_{max} approximately 2.6-times higher than the concentration observed prior to the evening oral dose on day 1 (C_{trough}). With a known terminal half-life of ~13 h, lacosamide plasma concentration from the end of infusion to just prior to the evening oral dose would be expected to decrease by a factor of 1.9 rather than 2.6, suggesting that the distribution effect of lacosamide may not be complete due to rapid input into the central circulation. A similar effect on C_{max} was observed in a phase 1 trial (SP645) following a single 15-min infusion of intravenous lacosamide 200 mg. Comparison of C_{trough} values observed in this trial with those of an unpublished double-blind, placebo-controlled phase 1 pharmacokinetic trial of lacosamide 200 mg/day (SP620) further supports the observation that a single loading dose two-times the oral maintenance dose (infused over 15 min) achieves near steady-state plasma concentrations of lacosamide. Given that the elimination half-life of the unchanged drug is ~13 h, administration of a fixed oral dose every 12 h would require approximately 3 days to reach steady-state peak and trough concentrations if a loading dose is not administered. The results of this trial show that a near steady-state plasma concentration can be reached directly at the end of a single 15-min infusion of an intravenous loading dose of two times the oral lacosamide maintenance dose.

Lacosamide (oral or intravenous) is currently recommended to be initiated at 50 mg b.i.d. and increased by 50 mg b.i.d. each week to the final recommended maintenance dose of 100–200 mg b.i.d. (200–400 mg/day). The data from this trial support the safety and tolerability of intravenous lacosamide initiation in lacosamide-naive patients at 200 or 300 mg under normal circumstances or up to 400 mg when rapid loading is important. For patients >60 years of age and for those with cardiac dysfunction, the safety and tolerability of a single intravenous lacosamide loading dose cannot be inferred from the results presented here, as such patients were excluded from the trial. Achievement of an effective dose of an AED as quickly as possible is important for some patients with partial-onset seizures whose seizures are not controlled with their current therapy. Initiating lacosamide treatment with a single intravenous loading dose may enable a patient to achieve steady state plasma concentrations associated with a therapeutic dose faster than with the recommended oral titration.

The trial design did not include stratification for concomitant AED/and or mechanism of action of concomitant AEDs across the cohorts. The trial enrolled 75 patients who were taking a sodium channel blocking AED [SCB(+)] and 25 patients who were taking a non–sodium-channel blocking AED [SCB(−)]; the percentage of patients in each of those AED groups varied between dosing cohorts. When the most common TEAEs across all cohorts were examined, there was no significant association (chi-square test $p = 0.753$) between TEAEs and concomitant AED group; however, some TEAEs were reported at slightly higher frequencies for patients taking concomitant SCB(+) AEDs. The better predictor of the common AEs for this trial was lacosamide dose, as common TEAEs increased with dose for both patients concomitantly taking either SCB(+) or SCB(−) AEDs.

These findings have important implications for future research. A retrospective study has been published in which intravenous lacosamide has been given for status epilepticus (Kellinghaus et al., 2011); however, there has been no systematic study for its use in this circumstance, and lacosamide is not approved for treatment of status epilepticus. Patients with status epilepticus often have significant medical problems, whereas the current study excluded patients with clinically significant medical problems. Therefore, future research should systematically examine whether rapid loading of intravenous lacosamide is safe and effective for treatment of status epilepticus, acute repetitive seizures, and other seizure emergencies.

In conclusion, administration of a single 15-min loading dose of intravenous lacosamide (200, 300, or 400 mg) followed by equivalent oral lacosamide maintenance for 6.5 days supports the feasibility of rapid initiation of adjunctive lacosamide treatment in lacosamide-naive POS patients taking one to two AEDs who require additional treatment. Further studies are needed to determine the safety and efficacy of rapid loading of lacosamide for seizure emergencies.

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