# Efficacy, Safety, and Pharmacokinetics of Lacosamide in Neonates With Seizures: Results of a Phase II/III, Open-Label, Randomized, Active Comparator Trial


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## Background

- Seizures occur more often during the neonatal period than at any other time during life.[1]
- Current intravenous treatments for neonatal seizures include phenobarbital, phenytoin, levetiracetam, lidocaine, and midazolam.[2]
  - Phenobarbital is the only treatment for neonatal seizures that is currently approved in certain regions.
- In the United States, lacosamide (LCM) is approved for the treatment of focal seizures in patients ≥1 month of age and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients ≥4 years of age.[3]
  - Indications and minimum age may differ for other countries.

## Objective

- To evaluate the efficacy, safety, and pharmacokinetics (PK) of LCM in neonates with repeated electroencephalographic neonatal seizures (ENS).

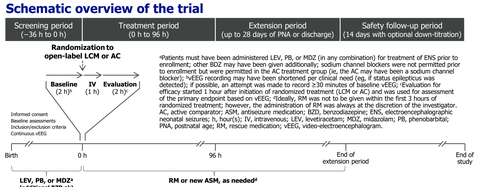
## Methods

### TRIAL DESIGN

- SP0968 (ClinicalTrials.gov: NCT04519645) was a Phase II/III, multicenter, open-label, randomized trial to evaluate the efficacy, safety, and PK of LCM in neonates with repeated ENS compared with an active comparator (AC).
- Patients were randomized 1:1 (stratified by seizure severity) to LCM 15 mg/kg/day (5 mg/kg every 8 hours via 30-minute intravenous infusions) or an AC (chosen based on standard of care per the local practice and treatment guidelines).
- Key inclusion criteria: ≥34 and <46 weeks of corrected gestational age, <28 days of postnatal age (PNA), weight ≥2.3 kg, video-electroencephalogram (vEEG) confirmation of ≥2 minutes of cumulative ENS[a] or ≥3 identifiable ENS prior to entering the treatment period despite previous antiseizure medication treatment.

[a]Defined as a seizure lasting for ≥10 seconds on vEEG.

### Schematic overview of the trial




[b]Patients must have been administered LEV, PB, or MDZ (in any combination) for treatment of ENS prior to enrollment; other BDZ may have been given additionally; sodium channel blockers were not permitted prior to enrollment but were permitted in the AC treatment group (ie, the AC may have been a sodium channel blocker); [c]vEEG recording may have been shortened per clinical need (eg, if status epilepticus was detected); if possible, an attempt was made to record ≥30 minutes of baseline vEEG; [d]Evaluation for efficacy started 1 hour after initiation of randomized treatment (LCM or AC) and was used for assessment of the primary endpoint based on vEEG; [e]Ideally, RM was not to be given within the first 3 hours of randomized treatment; however, the administration of RM was always at the discretion of the investigator. AC, active comparator; ASM, antiseizure medication; BZD, benzodiazepine; ENS, electroencephalographic neonatal seizures; h, hour(s); IV, intravenous; LEV, levetiracetam; MDZ, midazolam; PB, phenobarbital; PNA, postnatal age; RM, rescue medication; vEEG, video-electroencephalogram.

- Screening (≤36 hours) was followed by a 96-hour treatment period; patients who benefited from randomized treatment could continue in an extension period (up to 28 days PNA); patients who discontinued at any time entered a 14-day safety follow-up.
- Rescue medication (RM)[a] could be administered if needed; however, patients were excluded from the primary efficacy analysis if this occurred within 3 hours after the first dose and were treated as non-responders for responder outcomes.

[a]Defined as any treatment initiation with a new ASM, or any increase of dose or frequency of an existing concomitant ASM for the treatment of seizures during the treatment period. ASM, antiseizure medication.

### STATISTICS

- The Safety Set (SS) included all enrolled patients who received ≥1 dose of treatment and was analyzed as treated.
- The Full Analysis Set (FAS) consisted of all patients in the SS with interpretable vEEG data from both the baseline and evaluation periods and was analyzed as randomized.
- The Per-Protocol Set (PPS) included all patients in the FAS who did not have important protocol deviations related to efficacy.
- The Pharmacokinetic PPS (PK-PPS) consisted of all patients who provided ≥1 measurable serum sample (with recorded sampling time) on ≥1 post-baseline visit with documented study drug intake times.
- Variables were summarized using descriptive statistics; for serum concentrations, the geometric mean (GeoMean) and coefficient of variation are also presented.

### OUTCOMES

- The primary outcome was reduction in seizure burden (defined as total minutes of ENS per hour) from baseline vEEG (−2 to 0 hours before treatment initiation) to evaluation period vEEG (1-3 hours after treatment initiation).
- Secondary outcomes included other efficacy outcomes, the incidence of treatment-emergent adverse events (TEAEs), and mean serum concentrations of LCM.

## Overview

### QUESTION

What are the efficacy, safety, and pharmacokinetics of lacosamide (LCM) in neonates with repeated electroencephalographic neonatal seizures (ENS)?

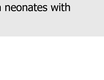
### INVESTIGATION

SP0968 (NCT04519645) was a Phase II/III, multicenter, open-label, randomized, active comparator trial in neonates (≥34 and <46 weeks of corrected gestational age; <28 days of postnatal age; weight ≥2.3 kg) with video-electroencephalogram confirmation of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS despite previous antiseizure medication treatment.

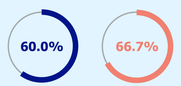
### RESULTS

**Efficacy (FAS)**

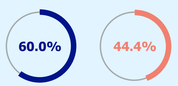
Median reduction in seizure burden from baseline to evaluation period



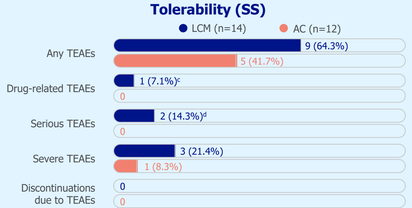

Response[a] during the evaluation period




≥80% response[b] during the evaluation period

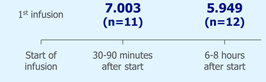



**Tolerability (SS)**




**Pharmacokinetics (PK-PPS)**

GeoMean (µg/mL)




[a]Response was defined as ≥50%/≥80% reduction in seizure burden from baseline to evaluation period in patients with severe/non-severe seizure burden at baseline (determined by investigator); [b]Response was defined as ≥80% reduction in seizure burden from baseline to evaluation period; [c]One patient had 2 drug-related TEAEs (convulsion and lethargy); [d]Two patients had a single serious TEAE each (congenital central nervous system anomaly and cerebral infarction). AC, active comparator; GeoMean, geometric mean; TEAE, treatment-emergent adverse event.

### CONCLUSIONS

In this randomized clinical trial of LCM in neonates, LCM treatment reduced seizure burden and was well tolerated.
Although LCM exposure tended to be higher in neonates, serum concentrations partially overlapped with exposure in adults at a dose of 400 mg/day LCM (without use of inducers).

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## Results

### PATIENT DISPOSITION AND DEMOGRAPHICS

- 29 patients were randomized; of these, 26 patients received ≥1 dose of treatment (SS).
  - 14 patients received LCM and 12 patients received AC.
  - The AC treatments received were phenobarbital (5 [41.7%]), fosphenytoin (5 [41.7%]), and levetiracetam (2 [16.7%]).
- Although 15 patients were randomized to LCM, 1 patient received AC rather than LCM.
  - This patient was included in the AC SS (as per actual treatment) and in the LCM FAS (as per randomized treatment).
- One patient (8.3%) in the AC treatment group discontinued the trial (primary reason: consent withdrawn; SS).

**Baseline demographics (SS)**

| | AC (n=12) | LCM (n=14) | ALL PATIENTS (N=26) |
|---|---|---|---|
| **Postnatal age, mean (SD), days** | 3.1 (2.8) | 4.1 (5.0) | 3.7 (4.1) |
| **Gestational age, mean (SD), weeks** | 39.82 (1.24) | 38.91 (2.20) | 39.33 (1.85) |
| **Female, n (%)** | 7 (58.3) | 7 (50.0) | 14 (53.8) |
| **Seizure burden severity,[a] n (%)** | | | |
| **Severe** | 4 (33.3) | 6 (42.9) | 10 (38.5) |
| **Non-severe** | 8 (66.7) | 8 (57.1) | 16 (61.5) |

[a]Determined at baseline by the investigator. AC, active comparator.

### RESCUE MEDICATION

- Overall, 10 patients (38.5%) received RM during the treatment period, most commonly (≥10% of patients) levetiracetam (23.1%) and phenobarbital (19.2%).
  - Five patients in each treatment group received RM (SS).

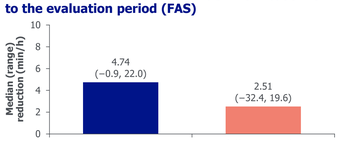
### EXPOSURE

- Mean exposure duration was 34.5 hours in the AC treatment group and 199.4 hours in the LCM treatment group (SS).[a,b]

[a]AC includes injections or infusions, whereas LCM includes infusions and oral tablets; [b]Study medication duration included dosing during the treatment period, extension period, and down-titration; more patients receiving LCM entered the extension period following completion of the treatment period.

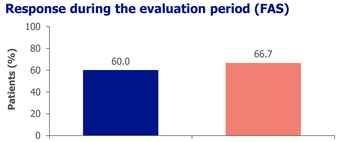
### EFFICACY

**Median reduction in seizure burden from baseline to the evaluation period (FAS)**




Percentages are based on the number of patients with data available for the evaluation period. Patients who received rescue medication at any time between first dose and 3 hours after first dose were excluded from the analysis.

**Response during the evaluation period (FAS)**

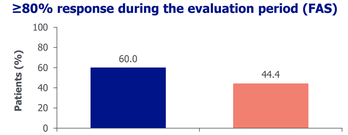



Percentages are based on the number of patients with data available for the evaluation period. Response was defined as ≥50%/≥80% reduction in seizure burden from baseline to evaluation period in patients with severe/non-severe seizure burden at baseline (determined by investigator). Patients who received rescue medication at any time between first dose and 3 hours after first dose were regarded as non-responders.

- Among patients with available data, 10 of 13 (76.9%) patients in the LCM group and 4 of 6 (66.7%) patients in the AC group were responders between 47 and 48 hours in the treatment period.

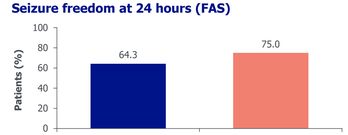
Response was defined as ≥50%/≥80% reduction in seizure burden from baseline to evaluation period in patients with severe/non-severe seizure burden at baseline (determined by investigator). Patients who received rescue medication at any time between first dose and 48 hours after first dose were regarded as non-responders.

**≥80% response during the evaluation period (FAS)**




Percentages are based on the number of patients with data available for the evaluation period. Response was defined as ≥80% reduction in seizure burden from baseline to evaluation period. Patients who received rescue medication at any time between first dose and 3 hours after first dose were regarded as non-responders.

**Seizure freedom at 24 hours (FAS)**




Percentages are based on the number of patients with data available at 23-24 hours. Seizure freedom was defined as having no seizures in the assessment period (23-24 hours after first dose); patients who received rescue medication at any time between first dose and 24 hours after first dose were regarded as not seizure-free.

- Among patients without RM use in the PPS (LCM: n=9; AC: n=7), the median reduction of seizure burden from baseline to evaluation period was 8.57 min/h (range: 1.2-22.0) with LCM and 2.51 min/h (range: −32.4-16.2) with AC.

### SAFETY AND TOLERABILITY

**Treatment-emergent adverse events (SS)**

| PATIENTS, n (%) [#] | AC (n=12) | LCM (n=14) | ALL PATIENTS (N=26) |
|---|---|---|---|
| **Any TEAE** | 5 (41.7) [21] | 9 (64.3) [21] | 14 (53.8) [42] |
| **Drug-related TEAEs[a]** | 0 | 1 (7.1) [2] | 1 (3.8) [2] |
| **Serious TEAEs** | 0 | 2 (14.3) [2] | 2 (7.7) [2] |
| **Severe TEAEs** | 1 (8.3) [1][b] | 3 (21.4) [3][c] | 4 (15.4) [4] |
| **Discontinuations due to TEAEs** | 0 | 0 | 0 |
| **Deaths (TEAEs leading to death)** | 0 | 1 (7.1) [1] | 1 (3.8) [1] |
| **TEAEs[d] reported for ≥2 patients overall** | | | |
| **Vomiting** | 1 (8.3) [1] | 2 (14.3) [2] | 3 (11.5) [3] |
| **Adrenal insufficiency** | 1 (8.3) [1] | 1 (7.1) [1] | 2 (7.7) [2] |
| **Convulsion** | 0 | 2 (14.3) [2] | 2 (7.7) [2] |
| **Feeding disorder neonatal** | 1 (8.3) [1] | 1 (7.1) [1] | 2 (7.7) [2] |

[a]Considered related to study drug by the investigator; [b]Cerebral ischemia; [c]Three patients had a single severe TEAE each (congenital CNS anomaly, cerebral infarction, and pulmonary edema); [d]Medical Dictionary for Regulatory Activities Version 16.1 Preferred Term. AC, active comparator; CNS, central nervous system; TEAE, treatment-emergent adverse event.

- In the AC group, 5 (41.7%) patients had 21 TEAEs.
- In the LCM group, 9 (64.3%) patients had 21 TEAEs.
  - One patient (7.1%) in the LCM group had 2 drug-related TEAEs (convulsion[a] and lethargy).

[a]Reported terms were 'recurrence of seizures' and 'weaning scheme too fast'.

  - Two (14.3%) patients in the LCM group had a single serious TEAE each (congenital central nervous system anomaly and cerebral infarction).
- One patient in the LCM group died during the study (due to congenital central nervous system anomaly); this TEAE was not considered related to study drug by the investigator.

### PHARMACOKINETICS

**LCM serum concentrations (µg/mL) after infusion (PK-PPS)**

| TIME WINDOW | n | GeoMean (Geo 95% CI) | GeoCV (%) |
|---|---|---|---|
| **30-90 min after start of 1st infusion** | 11 | 7.003 (5.486, 8.940) | 37.6 |
| **6-8 h after start of 1st infusion** | 12 | 5.949 (4.695, 7.539) | 38.6 |
| **30-90 min after start of 2nd or 3rd infusion** | 11 | 13.27 (10.94, 16.10) | 29.4 |
| **6-8 h after start of 2nd or 3rd infusion** | 13 | 9.607 (7.619, 12.11) | 39.8 |

CI, confidence interval; Geo, geometric; GeoCV, geometric coefficient of variation; GeoMean, geometric mean; h, hours; min, minutes.

- The GeoMean serum concentration of LCM was 7.003 µg/mL at 30-90 minutes (n=11) and 5.949 µg/mL at 6-8 hours (n=12) after start of 1st infusion.
  - A similar trend was observed after the 2nd or 3rd infusion of LCM, but concentrations were increased due to accumulation.
- Interparticipant variability was <40%.

## Conclusions

- In this randomized clinical trial of LCM in neonates, LCM treatment reduced seizure burden and was well tolerated.
  - During the evaluation period, patients randomized to LCM and AC both experienced reductions in seizure burden, with a numerically higher proportion of patients in the LCM group than in the AC group having ≥80% response.
  - The safety results observed in neonates were consistent with the known safety profile of LCM in older children and adults with epilepsy.
- Although LCM exposure tended to be higher in neonates, serum concentrations partially overlapped with exposure in adults at a dose of 400 mg/day LCM (without use of inducers).

## Limitation

- Interpretation of efficacy results is limited by the small number of patients.

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