CLINICAL STUDY REPORT SYNOPSIS: SP902

Name of company: UCB Pharma	**Individual study table referring to part of the dossier**: Not applicable	*(For National Authority Use Only)*
Name of finished product: Lacosamide	**Volume**: Not applicable	
Name of active ingredient: SPM 927 (lacosamide [LCM])	**Page:** Not applicable	

Title of study: A Historical-controlled, Multicenter, Double-blind, Randomized Trial to Assess the Efficacy and Safety of Conversion to Lacosamide 400mg/day Monotherapy in Subjects with Partial-onset Seizures

Investigator(s): 160 investigators enrolled subjects in the study.

Study site(s): This was a multicenter study that included 160 sites in the US, Canada, Europe, and Australia.

Publication(s) (reference[s]): None

Studied period: approximately 5 years, 4 months **First subject enrolled:** 02 Aug 2007 **Last subject completed:** 06 Dec 2012	**Phase of development:** Phase 3

Objective(s): The objective of this study was to demonstrate the efficacy and safety of conversion to LCM 400mg/day monotherapy for partial-onset seizures (with or without secondary generalization) in subjects 16 to 70 years of age who were withdrawn from 1 to 2 marketed antiepileptic drugs (AEDs).

Methodology: SP902 was a historical-controlled, multicenter, double-blind, randomized, conversion to monotherapy study designed to assess the efficacy and safety of LCM 400mg/day (200mg twice daily) monotherapy in subjects 16 to 70 years of age with partial-onset seizures, including secondary generalized seizures (heretofore referred to as partial-onset seizures). A LCM 300mg/day (150mg twice daily) arm was added to blind the treatment group and to ensure a study design consistent with the historical-control studies on which SP902 was based. Subjects who met the inclusion criteria and were taking stable doses of 1 or 2 marketed AEDs during the 56-day (8-week) Baseline Phase were randomized in a double-blind 3:1 scheme to either LCM 400mg/day or 300mg/day, respectively. During the 3-week Titration Phase, dose titration began at LCM 200mg/day. Lacosamide was titrated in 100mg/week steps to 300 or 400mg/day. Once the subject reached the end of the 3-week Titration Phase, the subject began the Maintenance Phase of the study. The Maintenance Phase was composed of a 6-week period for withdrawal of background AEDs, followed by a 10-week Monotherapy Phase at the targeted LCM dose. One dose reduction was allowed during the 16-week Maintenance Phase if the subject was unable to tolerate the randomized target dose (ie, LCM 400mg/day→LCM 300mg/day or LCM 300mg/day→LCM 200mg/day). A subject must have taken at least 1 dose of

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Maintenance Phase study medication in order to qualify for the dose reduction.

At the end of 16 weeks, subjects were offered the option of entering an open-label study (SP904). Subjects who chose to enroll in the open-label study entered a 1-week Transition Phase in which their study medication was transitioned to a dose of LCM 300mg/day or LCM 400mg/day in a manner which did not unblind the subject's randomized treatment assignment.

Subjects completing the Maintenance Phase who chose not to enroll in the open-label study entered a 1-week Taper Phase if not initiating treatment with commercial LCM. Background AEDs (1 to 2) may have been reintroduced/initiated at the beginning of this Taper Phase at the discretion of the investigator.

Taper of LCM was not required for subjects who completed or withdrew from the study and who, in consultation with the investigator, chose to initiate treatment with commercial LCM rather than to participate in the open-label extension study. These subjects entered a 1-week Transition Phase. At the end of this Transition Phase, subjects had a Final Clinic Visit, which was the last scheduled study visit for these subjects.

Subjects who entered the Maintenance Phase but were withdrawn due to meeting an exit criterion were eligible to participate in the open-label extension study. The decision to enroll these subjects into the open-label study was made after discussion with the medical monitor. These subjects entered a 1-week Transition Phase in which their study medication was transitioned to a dose of LCM 300mg/day or LCM 400mg/day in a manner which did not unblind the subject's randomized treatment assignment.

Subjects who discontinued the study during the Maintenance Phase for any other reason other than meeting exit criteria or who met exit criteria and chose not to enter the open-label extension study entered a 1-week Taper Phase (for subjects requiring a longer taper, the investigator should have contacted the medical monitor to discuss). Background AEDs (1 to 2) may have been reintroduced/initiated at the beginning of this Taper Phase at the discretion of the investigator.

The maximum duration of a subject's study participation was 30 weeks. The maximum duration of study medication administration was 20 weeks.

Number of subjects (planned and analyzed): A sample size of 338 subjects in the LCM 400mg/day group was to provide approximately 90% power for the comparison of the Kaplan-Meier estimate for the percentage of subjects exiting by Day 112 of the Maintenance Phase vs a fixed historical-control exit rate. This sample size calculation was based on a 1-sided, 0.025 significance level, an assumed 0.55 exit rate for the LCM 400mg/day dose group, and a 0.653 exit rate for the historical control. Other assumptions included a 10% dropout rate (for

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nonexit criteria reasons) during the Maintenance Phase and a 20% dropout rate during the Titration Phase. It was expected that at least 270 subjects randomized to LCM 400mg/day would enter the Maintenance Phase.

A total of 425 randomized subjects received treatment and were included in the Safety Set (SS). Of those in the SS, 383 entered the Maintenance Phase by beginning the withdrawal of Baseline AEDs and were included in the Full Analysis Set (FAS). Within the FAS, 239 subjects had no important protocol deviations related to efficacy and were included in the Per-Protocol Set (PPS). One subject was randomized at 2 sites; he is summarized once in the Enrolled Set (ES; for a randomized total of N=426), but was excluded from the SS (for a total of N=425).

Diagnosis and main criteria for inclusion: To be eligible to participate in this study, subjects must have been 16 to 70 years of age (inclusive) with a diagnosis of epilepsy with simple partial seizures (motor component) and/or complex partial seizures (with or without secondary generalization) according to the International Classification of Epileptic Seizures, 1981. Subjects must have been maintained on a stable dose of 1 or 2 marketed AEDs for at least 28 days prior to Visit 1 and during Baseline (if a subject was on 2 AEDs, the second AED must have been ≤50% of the minimum recommended maintenance dose per USA product label at Visit 1 and during Baseline when used as an adjunctive therapy). Subjects must have reported a minimum seizure frequency during the 8-week Baseline Phase of 2 partial-onset seizures (IA, IB, or IC) per 28 days. In the case of simple partial seizures, only those with motor signs (IA1) were counted towards meeting this inclusion criterion. Subjects must have had ≤40 partial seizures (ie, IA1, IA2, IA3, IA4, IB, IC) per 28 days during the 8 week Baseline Phase.

Subjects were not eligible if they had a seizure disorder characterized primarily by isolated auras (ie, simple partial seizures without observable motor signs). Subjects were not eligible if they had a history of primary generalized or unclassified seizures, a history of status epilepticus within the 12-month period prior to Visit 1, or a history of cluster seizures (defined as bouts of increased seizures which could not be reliably counted, but which did not represent status epilepticus, during the 8-week period prior to Visit 1 and during the 8-week Baseline Phase. Subjects who had a seizure-free period ≥28 consecutive days during the 8-week Baseline Phase were not eligible. Subjects who had received treatment with benzodiazepines, phenobarbital, or primidone within 28 days prior to Visit 1 or during Baseline were not eligible. Subjects who were taking 1 or more of the following medications on a regular basis within 28 days prior to Visit 1 or during Baseline were not eligible: neuroleptics, monoamine oxidase inhibitors, barbiturates, or narcotic analgesics.

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Test product, dose(s) and mode of administration, batch number(s): Subjects who completed the Baseline Phase and continued to meet eligibility criteria entered the Titration Phase at Visit 3 and were randomized in a double-blind fashion in a 3:1 ratio to LCM 400mg/day or LCM 300mg/day. During the 3-week Titration Phase, dose titration began at LCM 200mg/day. Lacosamide was titrated in 100mg/week steps to LCM 300 or 400mg/day. All doses were administered orally. The batch numbers were as follows:

90209030002, 90209030004, 90207060001, 90208060001, 90208060003, 90208060004, BX1003312, BX1003327, BX1003361, BX1003374, BX1003904, BX1003922, BX1003943, BX1004971, BX1004987, BX1004988, BX1008076.

Duration of treatment: The total study duration, including the 8-week Baseline Phase, the 3-week Titration Phase, the 6-week AED Withdrawal Phase, the 10-week Monotherapy Phase, the 1-week Taper/Transition Phase, and the 2-week Safety Follow-Up Phase, was 30 weeks.

Reference therapy, dose(s) and mode of administration, batch number(s): None

Criteria for evaluation:

Efficacy: The primary efficacy variable was the percentage of subjects identified as meeting at least 1 of the following exit criteria by Day 112 relative to the start of the withdrawal of background AEDs:

1. A 2-fold or greater increase in average monthly (28-day) partial-onset seizure frequency (motor and nonmotor) compared to average monthly partial-onset seizure frequency (motor and nonmotor) during the Baseline Phase.
2. A 2-fold or greater increase in consecutive 2-day partial-onset seizure frequency (motor and nonmotor) vs the highest consecutive 2-day partial-onset seizure frequency (motor and nonmotor) that occurred during the Baseline Phase.

   Note: If the highest consecutive 2-day partial-onset seizure frequency during the Baseline Phase was 1, a 2-day partial-onset seizure frequency of ≥3 was required to meet this exit criterion.
3. Occurrence of a single generalized tonic-clonic seizure if none had occurred in the 6 months prior to randomization.
4. A prolongation or worsening of overall seizure duration, frequency, type or pattern considered by the investigator as serious enough to warrant study discontinuation.
5. Status epilepticus or new onset of serial/cluster seizures.

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Secondary efficacy variables included the following:

- Time to first occurrence of any exit event
- The sum of the exit event rate, the withdrawal due to adverse event (AE) rate, and the withdrawal due to lack of efficacy rate
- Duration of monotherapy treatment (days) during the Monotherapy Phase
- Clinical Global Impression of Change (CGIC) at study termination or completion
- Patient's Global Impression of Change (PGIC) at study termination or completion

Pharmacokinetics: LCM and desmethyl LCM plasma concentrations were presented by gender, visit, and dose, as well as normalized by daily dose.

Safety: Safety variables included the following:

- AEs as reported spontaneously by the subject and/or caregiver or observed by the investigator
- Subject withdrawal due to AEs
- Hematology, blood chemistry, and urinalysis parameters
- 12-lead electrocardiograms (ECGs)
- Vital sign measurements (ie, blood pressure, pulse rate)
- Physical and neurological examination findings
- Body weight

Statistical methods: Inferential efficacy analysis was performed and summarized for the LCM 400mg/day treatment group only. All secondary efficacy parameter summaries were presented descriptively for both the LCM 300mg/day and LCM 400mg/day treatment groups. Safety parameters were summarized for both treatment groups and overall.

The analysis set for subject disposition was based on the ES. The analysis set for safety variables was the SS. The analysis sets for efficacy variables were the FAS and PPS.

The primary efficacy variable was the percentage of subjects meeting at least 1 exit criterion by Day 112 of the Maintenance Phase, where Day 112 was relative to the start of withdrawal of background AEDs (eg, the start of the Maintenance Phase).

The Kaplan-Meier estimate of the percentage of subjects meeting at least 1 exit criterion by Day 112 (cumulative exit rate) and a 2-sided 95% confidence interval (CI) for this estimate was calculated for the LCM 400mg/day dose group for the FAS. In the case of subjects meeting more

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than 1 exit criterion, the date of the earliest exit was used in the calculation of the Kaplan-Meier estimate.

The upper limit of the CI for the estimate of the LCM 400mg/day exit rate was compared with a prespecified historical-control exit rate of 0.653; hereafter referred to as the historical-control exit rate. The LCM 400mg/day dose group would be declared an effective withdrawal to monotherapy treatment if the upper 95% confidence limit for the estimate of the exit rate was less than 0.653.

Primary Hypothesis:

H_0: 1 – S(t) = 0.653

H_A: 1 – S(t) <0.653,

where S(t) was the cumulative rate of subjects who had not met an exit criteria by Day 112 of the Maintenance Phase (ie, survival rate at Day 112).

The 0.653 historical-control exit rate referenced above was based on the lower limit of a 2-sided 95% prediction interval for an estimate of the combined pseudo-placebo exit rate (controlling for inter-study variability) from a meta-analysis of a set of historical withdrawal to monotherapy studies with similar design as SP902. The 95% prediction interval for the historical control provides 97.5% confidence that a single repeated study would yield a pseudo-placebo exit rate of 0.653 or higher.

Up to 10% of subjects in the LCM 400mg/day group who withdrew from the study on or before Day 112 of the Maintenance Phase for nonexit criteria reasons (and not otherwise programmatically determined to meet an exit criterion) were to be censored as of the last Maintenance Phase dose. (Censoring means that a subject who dropped out prematurely was included in the denominator for the estimate of the cumulative percentage exiting for the time the subject was at risk in the study and known to not have had an exit event).

The 10% of subjects to be censored were to be based on a random sample of all subjects prematurely discontinuing in the LCM 400mg/day group during the Maintenance Phase due to nonexit criterion reasons (and not otherwise programmatically determined to be an exit). Subjects prematurely discontinuing during the Maintenance Phase who were not included in the randomly selected 10% were to be counted as having met an exit criterion. (The early termination rate [due to nonexit criteria reasons] during the Maintenance Phase for the LCM 400mg/day group for the FAS was expected to be ≤10%. This expected early termination rate [due to nonexit criteria reasons] is consistent with that observed in the pooled historical-control data [and these subjects were censored in the analysis resulting in the historical-control, pseudo-placebo exit rate].)

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The Kaplan-Meier estimate of the LCM 400mg/day exit rate and the associated 95% CI were presented. Additionally, the number and percentage of subjects meeting at least 1 exit criterion by Day 112 of the Maintenance Phase were summarized overall and by exit criterion. The Kaplan-Meier estimate over time figure was also provided for the LCM 400mg/day and LCM 300mg/day treatment groups.

No imputation for missing seizure diary data was performed when deriving exit criterion 1 or 2 because the primary efficacy analysis must have been consistent with the analyses from which the historical control was derived. The impact of missing data on the determination of whether or not a subject met an exit criterion was evaluated through sensitivity analyses.

Summary and conclusions:

Subject disposition: A total of 787 subjects were screened at 160 sites. There were 378 screen failures (48.0%) primarily attributed to ineligibility (28.1% due to inclusion criteria not met and 34.7% due to exclusion criteria met). A total of 426 individual subjects (54.1%) were randomized (320 to LCM 400mg/day and 106 to LCM 300mg/day). Of the 425 individual subjects randomized and included in the SS, 263 subjects (61.9%) completed the study. One subject was randomized at 2 sites; he is summarized once in the ES (for a randomized total of N=426), but was excluded from the SS (for a total of N=425).

Overall, during the Treatment Phase, the most common reason for discontinuation was AE (72 subjects; 16.9%), followed by lack of efficacy (41 subjects; 9.6%) and protocol deviation (17 subjects; 4.0%).

By study phase, the most common reasons for discontinuation from the Titration Phase were AE and protocol deviation (5.2% and 1.9%, respectively); from the AED Withdrawal Phase were AE and lack of efficacy (5.4% and 2.8%, respectively); and from the Monotherapy Phase were lack of efficacy and AE (6.8% and 6.1%, respectively).

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Efficacy results: The primary efficacy endpoint was the cumulative exit rate at Day 112 of the Maintenance Phase, where Day 112 was relative to the start of withdrawal of background AEDs (eg, the start of the Maintenance Phase) evaluated for subjects in the LCM 400mg/day group.

- The Kaplan-Meier estimate of the percentage of subjects meeting at least 1 exit criterion by Day 112 (cumulative exit rate) for the LCM 400mg/day group was 0.300 (95% CI: 0.246, 0.355). The upper limit of the 2-sided 95% CI for this estimate was 0.355, indicating the predicted exit rate is statistically significantly lower than the historical-control exit rate (0.653); and thus, superiority of LCM 400mg/day over historical control was demonstrated.
- Supportive analyses, conducted on the primary endpoint to evaluate the robustness of the effect of LCM 400mg/day, demonstrated that the cumulative exit rate was lower than that of the historical-control exit rate for the PPS and for analysis with no censoring limit.
- Sensitivity analyses, requested by the Food and Drug Administration (FDA), conducted on the primary endpoint demonstrated the cumulative exit rate was lower than that of the historical-control exit rate under each of the conditions tested:
  - The predicted exit rate in the LCM 400mg/day group with censoring of first enrollers (subjects in the LCM 400mg/day group who discontinued prematurely during the Maintenance Phase due to non-exit criteria reasons or had the shortest duration of time in the study)
  - Titration dropouts (to assess for the impact of subjects who did not complete the Titration Phase)
  - The predicted exit rate in the LCM 400mg/day group for US and North American subjects (as all subjects in the historical-control group were enrolled in North America and SP902 enrolled subjects in the US, Canada, Europe, and Australia)
  - Investigator reported exit criteria vs calculated exit criteria (as there were differences between investigator assessments and the algorithm used to calculate exit criterion 1)
  - Other sensitivity analyses were performed on the primary efficacy endpoint where the definitions of exit criteria 1, 2, and 3 were modified as requested by the FDA and where the exit rate due to all criteria except for exit criterion 4 (which may have been subjective) was evaluated. Results of these additional sensitivity analyses were supportive of the results of the primary efficacy analysis.

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- Other sensitivity analyses conducted on the primary endpoint also demonstrated the cumulative exit rate was lower than that of the historical-control exit rate under each of the conditions tested:
  - Analysis with imputed missing data (to test for sensitivity to missing seizure diary data)
  - Analysis of the modified FAS
  - Analysis using study phases defined by visit dates.
- Exploratory evaluation of the influence of a predefined set of covariates on the predicted exit rate did not identify any covariates that were predictive of the exit rate at Day 112 for the LCM 400mg/day group.
- A further exploratory modeling simulation for the region covariate demonstrated that the upper 95% confidence limit for the predicted exit rate for the LCM 400mg/day group was less than that of the historical-control exit rate across the range of values for region in the model (0 to 100% representation from non-North American sites).
- The LCM 300mg/day (150mg twice daily) arm was included to blind the treatment group and to ensure a study design consistent with the historical-control studies on which SP902 was based. The exit rate in the LCM 300mg/day group demonstrated that the cumulative exit rate is lower than the lower bound for the 95% prediction interval for the historical control. The results from the exploratory analysis for the LCM 300mg/day group were similar to those for the LCM 400mg/day group.
- Subgroup analyses showed some descriptive differences in exit rates between subgroup values for age and race; however, differences were difficult to interpret given the small number of subjects in some of the age and race categories. Descriptive differences in the exit rate were also observed for different values of region. Subjects from sites outside of North America appeared to exit more often than subjects from North American sites. However, these descriptive differences did not appear to have a significant influence on the predicted exit rate in the Cox proportional hazards exploratory models for the LCM 400mg/day group.

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Secondary efficacy analyses demonstrated the following:

- In the analysis of the efficacy data, subjects were classified as having an exit event if they experienced at least 1 of 3 events during the Maintenance Phase (met an exit criterion, or withdrew prematurely due to an AE or lack of efficacy). Results from this analysis were comparable with the rate of exit in the LCM 400mg/day group for exit criteria alone.
- During the Maintenance Phase (starting with the AED Withdrawal Phase and including the Monotherapy Phase), the mean time to exit was 45.0 and 37.4 days, respectively, for subjects in the LCM 400mg/day and LCM 300mg/day groups.
- The mean durations of monotherapy were 64.2 and 64.3 days, respectively, for subjects in the LCM 400mg/day and LCM 300mg/day groups.
- With regard to global impressions of change, the majority of subjects in both treatment groups were reported to have an improved status (CGIC: 75.4% and 72.7% of subjects in the LCM 400mg/day and 300mg/day groups, respectively; PGIC: 74.3% and 72.7% of subjects in the LCM 400mg/day and 300mg/day groups, respectively).

Pharmacokinetics results: The LCM plasma concentration data separated by actual daily dose reflect that subjects were treated with active drug and almost all the resulting concentrations are within the expected ranges for LCM.

Typical LCM concentrations (after administration of multiple doses of LCM) have been previously published. Population PK evaluations have shown area under the curve (AUC) within a dosing interval at steady state during LCM therapy with a dose of 400mg/day (200mg twice a day) of about 110µg/mL*h corresponding to a mean concentration of 9µg/mL. These population PK evaluations have shown the slightly higher LCM concentrations in females than in males and are supportive of the SP902 PK results.

Pharmacokinetics of LCM after administration of multiple doses of 200mg twice a day in young male subjects resulted in an AUC of about 86µg/mL*h corresponding to a mean concentration of 7µg/mL.

Safety results: At doses of LCM 300mg/day and 400mg/day, LCM was safe and well tolerated when administered as conversion to monotherapy in subjects with partial-onset seizures.

With regard to treatment-emergent adverse events (TEAEs) coded to convulsions, investigators were instructed to report any change (including improvement) in seizure type, severity,

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frequency, or duration as an AE. A change to a less severe seizure type would be an improvement in the subject's condition; however, because the preferred term (PT) of convulsions captures both improvements and worsening of seizure conditions, the incidence of convulsion may be an overestimate of the number of subjects with worsening seizures.

- A total of 359 subjects (84.5%) reported 1834 TEAEs. Dizziness was the most commonly reported TEAE (24.0% of subjects), followed by headache (14.4%), nausea (13.4%), TEAEs coded to convulsion (11.5%), somnolence (10.4%), and fatigue (10.1%). There were no apparent differences between the LCM 400mg/day and LCM 300mg/day groups with the exceptions of dizziness which was reported at a higher incidence in the LCM 400mg/day group compared with the LCM 300mg/day group (26.0% vs 17.9%), and TEAEs coded to convulsion, which were reported at a lower incidence in the LCM 400mg/day group compared with the LCM 300mg/day group (10.0% vs 16.0%).
- The most commonly reported TEAEs during the 10-week Monotherapy Phase included TEAEs coded to convulsion (6.2%), followed by headache (5.6%), dizziness (4.7%), nasopharyngitis (4.4%), and anxiety (3.2%).
- Most reported TEAEs were considered mild or moderate in severity. Severe TEAEs were reported by 44 subjects (10.4%) overall.
- In general (with the exception of nausea), the percentage of subjects reporting the most frequent commonly reported TEAEs by dose at onset increased with increasing LCM dose; however, that may be due to the fact that subjects were more likely to be at doses of LCM 300mg/day or LCM 400mg/day for a longer period of time (the Treatment Phase) compared with lower doses during the shorter Titration Phase. The incidence of the onset of nausea was highest in the LCM ≥200 to <300mg/day group.
- A total of 250 subjects (58.8%) reported at least 1 TEAE considered related to LCM per investigator during the Treatment Phase. Overall, dizziness was the most commonly reported TEAE considered related to LCM (19.8%), followed by somnolence (9.2%) and headache (8.5%). In general, the incidence of TEAEs considered related to LCM was comparable for the 2 treatment groups. Differences included the incidence of TEAEs considered related to LCM in the system organ class (SOC) of Gastrointestinal disorders (21.6% in the LCM 400mg/day group vs 15.1% in the LCM 300mg/day group) and the incidence of somnolence (7.5% in the LCM 400mg/day group vs 14.2% in the LCM 300mg/day group).
- There were 3 deaths that occurred during the study (1 due to polytraumatism and 2 sudden unexpected deaths in epilepsy [SUDEPs]), all 3 of which were considered unrelated or

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unlikely related to study medication. Overall, 17 subjects (4.0%), all of whom were randomized to LCM 400mg/day, reported a total of 21 serious adverse events (SAEs). Events coded to convulsion were the most common SAEs during the Treatment Phase, reported by 5 subjects (1.2%). No other SAE was reported by more than 1 subject.

- Treatment-emergent AEs leading to discontinuation were reported in 69 subjects (16.2%); there were no apparent differences between treatment groups. Overall, TEAEs coded to convulsion were the most common TEAEs leading to discontinuation (8.2%), followed by dizziness (1.6%), grand mal convulsion (1.2%), and nausea (0.9%).
- There were 2 TEAEs reported that were considered other significant TEAEs: a mild TEAE of bradycardia considered unlikely related to study medication and a moderate TEAE of loss of consciousness considered possibly related to study medication (both of which resolved and no action was taken with study medication).
- The incidence of TEAEs of relevance to the partial-onset seizure population was low.
  - The most frequently reported seizure-related TEAE was coded to convulsion (49 subjects, 11.5%); the event was considered severe in 10 subjects (2.4%), related in 23 subjects (5.4%), serious in 7 subjects (1.6%), and led to discontinuation in 35 subjects (8.2%). Two additional subjects reported SAEs related to seizures (epilepsy and status epilepticus).
  - Thirteen subjects (3.1%) reported cognitive disorder, 10 subjects (2.4%) reported memory impairment, and 6 subjects (1.4%) reported amnesia. None of these events were serious; 1 led to study medication discontinuation (memory impairment).
  - There were no TEAEs of psychotic disorder, epileptic psychosis, or acute psychosis reported during the study.
  - Eight subjects (1.9%) reported weight increased and 2 subjects (0.5%) reported weight decreased. None of these events was serious or led to study medication discontinuation.
- There was no evidence for any effect of LCM treatment on laboratory parameters.
- There were no cases that met Hy's Law criteria for drug-induced liver injury or multiorgan hypersensitivity.
- There was no evidence for any effect of LCM treatment on vital signs, weight, ECG evaluations, physical examinations, or neurological examinations.

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- There were no AEs of suicidal ideation or suicidal behavior reported during this study.

There were 27 subjects who had only IC seizures. A higher percentage of subjects with only IC seizures discontinued from the study (55.6%) compared with those subjects who did not have only IC seizures (36.9%). A higher percentage of subjects with only IC seizures discontinued due to an AE (29.6%) compared with those subjects who did not have only IC seizures (16.1%); however, the small size of the IC-only group limits comparisons that can be made vs the not IC-only group. The 2 events of SUDEP were reported in subjects with only IC seizures.

Conclusions: The primary efficacy endpoint was the cumulative exit rate at 112 days after the beginning of the AED Withdrawal Phase, evaluated for subjects in the LCM 400mg/day group.

- In the FAS, the estimated rate of exit at Day 112 for LCM 400mg/day was significantly lower than that of the historical control based on the historical-control exit rate of 0.653, thus demonstrating superiority of LCM 400mg/day over historical-control.
- Sensitivity analyses, conducted on the primary endpoint to evaluate the robustness of the effect of LCM 400mg/day, demonstrated that the cumulative exit rate was lower than that of the historical control under each of the conditions tested.
- Exploratory analyses (adjustment for Baseline covariates and evaluation of the exit rate in the LCM 300mg/day group) supported the results of the primary analyses.
- Secondary efficacy analyses (mean time to exit and duration of monotherapy) confirmed the results of the primary analyses.

The results of the efficacy analyses demonstrate that the LCM 400mg/day dose was efficacious as withdrawal to monotherapy to subjects with partial-onset seizures.

Lacosamide, at doses of 400mg/day and 300mg/day, was safe and well tolerated when administered as monotherapy to subjects with partial-onset seizures, with an AE profile similar to that reported for LCM as adjunctive therapy.

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