CLINICAL STUDY REPORT SYNOPSIS: SP0993

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Title of study: A Multicenter, Double-blind, Double-dummy, Randomized, Positive-controlled Study Comparing the Efficacy and Safety of Lacosamide (200 to 600 mg/day) to Controlled Release Carbamazepine (400 to 1200mg/day), Used as Monotherapy in Subjects (≥16 years) Newly or Recently Diagnosed with Epilepsy and Experiencing Partial-onset or Generalized Tonic-clonic Seizures

Investigators: A total of 185 investigators enrolled subjects.

Study sites: A total of 185 sites in Australia, Canada, Europe, Japan, Mexico, Philippines, South Korea, Thailand, and USA participated (ie, enrolled subjects) in the study.

Publications (references): None

Study period: The study period was approximately 4 years 3 months. **First subject enrolled:** 27 Apr 2011 **Last subject completed:** 07 Aug 2015	**Phase of development:** Phase 3

Objective: The objective of this study was to compare the efficacy and safety of lacosamide (LCM; 200 to 600mg/day) to carbamazepine (controlled release) (CBZ-CR; 400 to 1200mg/day) used as monotherapy for at least 1 year, efficacy being measured as a primary endpoint by 6-month seizure freedom, in newly or recently diagnosed epilepsy subjects. The study employed a noninferiority design to show at least a similar benefit-risk balance for LCM compared with CBZ-CR, using 6-month seizure freedom as the primary endpoint in subjects ≥16 years of age dependent upon country requirements.

Methodology: SP0993 was a Phase 3, multicenter, double-blind, double-dummy, randomized, positive-controlled study comparing the efficacy and safety of LCM (200, 400, or 600mg/day) to CBZ-CR (400, 800, or 1200mg/day) used as monotherapy for up to a maximum of 121 weeks in subjects newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or generalized tonic-clonic seizures.

In accordance with Agency guidelines (CHMP/EWP/566/98, 2010 as revised), SP0993 employed a noninferiority design to show at least a similar benefit-risk balance for LCM compared with CBZ-CR.

The step-wise design for SP0993 employed 3 predefined target dose levels for both LCM and

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CBZ-CR. SP0993 initiated treatment with LCM 200mg/day or CBZ-CR 400mg/day after careful up-titration. In case this dose did not control the seizures during the Evaluation Phase, subjects had the opportunity for the dose to be increased to LCM 400mg/day or CBZ-CR 800mg/day, and if this dose did not control seizures, the dose was increased to LCM 600mg/day or CBZ-CR 1200mg/day.

If seizures occurred during the Up-titration and Stabilization Phase while the subject had not yet been stabilized on the assigned target dose, the subject did not need to be withdrawn from the study or the dose did not need to be increased, but the subject continued to receive study medication as planned until the Stabilization Visit. Throughout the study, seizures were recorded in the subject diary.

Number of subjects (planned and analyzed): A sample size of 439 randomized subjects per treatment arm would provide approximately 0.90 power for the comparison of the Kaplan-Meier (KM) estimates for the difference in proportion of subjects seizure free for the 26-week Evaluation Phase following stabilization at the last evaluated dose for LCM versus CBZ-CR. This sample size was based on a 2-group test for equivalence of proportions with a 0.05 significance level (2-sided), an assumed seizure-free rate for CBZ-CR of 0.60, and a noninferiority margin of -0.12 absolute difference. Other assumptions included a 20% rate of important protocol deviations resulting in removal from the Per Protocol Set (PPS).

A total of 888 subjects were randomized; 2 subjects withdrew consent after randomization and did not take any study medication. Eight hundred eighty-six randomized subjects received at least 1 dose of study medication and were included in the Safety Set (SS) and Full Analysis Set (FAS) (the SS and FAS represent the same subject populations). Within the FAS, 805 subjects were included in the PPS. Seventy-seven subjects were excluded from the PPS due to important protocol deviations related to primary efficacy. An additional 4 subjects at Site ▮ were excluded from the PPS due to findings of noncompliance with applicable regulations, Good Clinical Practices, and International Conference on Harmonisation guidelines. Four subjects from sites in the Ukraine and Crimea region were excluded from the PPS due to missing data as a result of political and civil unrest, which prohibited study-related activities.

Diagnosis and main criteria for inclusion: Subjects must have fulfilled the following inclusion criteria to be eligible to participate in this study:

1. An Institutional Review Board/Independent Ethics Committee approved written Informed Consent form (ICF) was signed and dated by the subject or by the parent(s) or legal representative. The Consent form or a specific Assent form, where required, was signed and dated by minors.

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2. Subject was willing and able to comply with all study requirements.

3. Subject was male or female and ≥16 years of age. Minors were included in some countries only if legally permitted.

4. Subject had newly or recently diagnosed epilepsy having experienced unprovoked partial-onset seizures (IA, IB, IC with clear focal origin) or generalized tonic clonic seizures (without clear focal origin) that were classifiable according to the International League Against Epilepsy Classification of Epileptic Seizures, 1981. The discrimination between IC and IIE was not requested for inclusion.

5. Subject had experienced at least 2 unprovoked seizures (separated by a minimum of 48 hours) in the 12 months preceding Visit 1 (Screening Visit) out of which at least 1 unprovoked seizure occurred in the 3 months preceding Visit 1.

6. Subject had an electroencephalogram (EEG) and a brain computed tomography (CT) scan or magnetic resonance imaging (MRI) exam of the brain within the past 12 months. If the EEG and brain CT scan or MRI exam were not performed prior to Visit 1, they needed to be completed and results must have been available prior to randomization at Visit 2.

Test product, doses and mode of administration, batch numbers: Subjects were randomized to a treatment arm (LCM or CBZ) in a 1:1 ratio. The randomization was stratified by the category for the number of seizures in the 3-month period prior to Visit 1 (≤2 seizures and >2 seizures).

Lacosamide was supplied as white, film-coated tablets, in doses of LCM 100mg and LCM 50mg and placebo for LCM was supplied as white film coated tablets. Study medication was orally administered twice daily (at approximately 12-hour intervals in the morning and in the evening) in 2 equally divided doses. The batch numbers for LCM were as follows:

BX1007780, BX1008174, BX1008178, BX1009105, BX1008181, BX1009104, BX1011762, BX1008180, BX1009106, BX1011772, BX1004314, BX1004341 BX1004347, BX1004340, BX1003096, BX1003095, BX1004348, BX1003098, BX1004418, BX1005847, and BX1004471.

The batch numbers for placebo for LCM were as follows:

BX1008234, BX1008143, BX1008147, BX1008142, BX1008144, BX1011767, BX1011763, BX1011765, BX1008411, BX1006113, BX1004315, BX1004316, BX1004317, BX1004318, BX1004419, BX1004420, BX1005840, BX1004423, and BX1005843.

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Duration of treatment: The study consisted of the following phases, with a maximum duration of 121 weeks (maximum duration of IMP administration was 118 weeks) for an individual subject:

- Screening Phase: 1 week

- Up-titration and Stabilization Phase: 3 weeks

- Evaluation Phase: 26 weeks

- Maintenance Phase: 26 weeks

- End of Study Phase: up to 7 weeks

Reference therapy, doses and mode of administration, batch numbers: Carbamazepine was supplied as yellow, opaque tablets, overencapsulated in double-blind capsules size A with an overfill mix of magnesium stearate and avicel, in a dose of CBZ-CR 200mg and placebo for CBZ-CR was supplied as yellow, opaque double-blind capsules size A with an overfill mix of magnesium stearate and avicel. Study medication was orally administered twice daily (at approximately 12-hour intervals in the morning and in the evening) in 2 equally divided doses. The batch numbers for CBZ-CR were as follows:

BX1008914, BX1010466, BX1012049, BX1012087, BX1004565, BX1004013, BX1004564, BX1005560, BX1005707, BX1006330, BX1006433, and BX1005708.

The batch numbers for placebo for CBZ-CR were as follows:

BX1008919, BX1010467, BX1011995, BX1008432, BX1004567, BX1004569, BX1004566, BX1004012, BX1005559, BX1005706, BX1005754, BX1005559, BX1006406, and BX1006522.

Criteria for evaluation:

Efficacy: The primary efficacy variable was the proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject.

Other efficacy variables included the following:

- Proportion of subjects remaining seizure free for 12 consecutive months (52 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject

- Time to first seizure or discontinuation due to adverse event (AE) or lack of efficacy (LOE) during 12 months of treatment following stabilization at the last evaluated dose for each subject

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- Time to first seizure or discontinuation during 12 months of treatment following stabilization at the last evaluated dose for each subject

- Time to first seizure during 12 months of treatment from the first dose of study medication

- Time to first seizure or discontinuation due to AE or LOE during 12 months of treatment from the first dose of study medication

- Time to first seizure or discontinuation during 12 months of treatment from the first dose of study medication

- Time to discontinuation due to AE or LOE during 12 months of treatment from the first dose of study medication

Exploratory: Exploratory variables were as follows:

- Clinical Global Impression of Change (CGIC)

- Patient's Global Impression of Change (PGIC)

- Health care resource use: additional health care provider visits unforeseen by the protocol, and hospitalizations

Pharmacokinetics/pharmacodynamics: The pharmacokinetic (PK) variables were as follows:

- Plasma concentrations of LCM and CBZ

Safety: The primary safety variables were as follows:

- AEs reported spontaneously by the subject and/or caregiver or observed by the investigator

- Subject withdrawals due to AEs

- Serious AEs (SAEs)

The other safety variables were as follows:

- Changes in hematology, chemistry, and urinalysis parameters

- Changes in 12-lead electrocardiograms (ECGs)

- Changes in vital sign measurements (ie, blood pressure and pulse rate)

- Changes in physical or neurological examination findings

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- Changes in body weight

- Changes in fasting serum lipid levels, and thyroid and sex hormone concentrations

Statistical methods:

Subject disposition, demographics, and Baseline epilepsy characteristics were summarized by treatment group and overall for the FAS and PPS.

Efficacy analyses

The primary efficacy analysis was a noninferiority assessment of LCM versus CBZ-CR for the proportion of subjects remaining seizure free for 6 months at the last evaluated dose. The primary efficacy assessment was based on the FAS and the PPS in accordance with European Medicines Agency Guidance, Points to Consider on Switching between Superiority and Noninferiority (CPMP/EWP/482/99, 2000), which states both populations are of equal importance.

The hypothesis for the assessment of primary efficacy was as follows:

H_0: $S(t)_{LCM} - S(t)_{CBZ-CR} \leq -0.12$

Versus

H_A: $S(t)_{LCM} - S(t)_{CBZ-CR} > -0.12$

where $S(t)$ (t=182 days) was the cumulative rate of subjects remaining seizure free for 6 months following stabilization at the last evaluated dose (also known as the survivorship function), and 0.12 represented the noninferiority margin based on absolute difference.

Estimation of treatment difference

Kaplan-Meier methods were used to estimate the proportion of subjects remaining seizure free for 6 months following stabilization at the last evaluated dose for each treatment group. The estimate for the difference in 6-month seizure freedom was adjusted for the past 3-month seizure count (≤ 2 and >2). The estimate for the stratified difference in proportion of subjects seizure free on LCM versus CBZ-CR and a corresponding 95% 2-sided confidence interval (CI) for LCM versus CBZ-CR ($CI_{LCM-CBZ}$) was produced using Mantel Haenszel methods. The stratified proportion of subjects remaining seizure free for at least 6 months in each treatment group and the associated variance were derived using Mantel Haenszel methods.

Noninferiority evaluation

The lower limit of $CI_{LCM-CBZ}$ was compared to the prespecified noninferiority margins of 0.12. If the lower limit of $CI_{LCM-CBZ}$ was >-0.12, noninferiority of LCM to CBZ-CR was demonstrated.

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Additionally, it was required that this lower confidence limit for the difference between LCM and CBZ-CR relative to the KM estimate of CBZ-CR 6-month seizure freedom rate be >20%. More specifically, the CBZ-CR rate needed to be sufficiently high so that the ratio of the lower limit of $CI_{LCM-CBZ}$ to the CBZ-CR seizure free rate multiplied by 100% was >-20%. Consequently, noninferiority was concluded if both of the following criteria were true:

- Lower limit of $CI_{LCM-CBZ} \times 100\% > -12\%$

- (Lower limit of $CI_{LCM-CBZ} / S_2) \times 100\% > -20\%$ (where S_2 is the CBZ-CR seizure free rate)

If the lower limit of $CI_{LCM-CBZ}$ was >0, there was evidence for superiority and a supporting p-value of the corresponding superiority test (2-sided, α=0.05) was given. The superiority test statistic, $Q = d^2/Var(d)$, was assessed by a chi-square distribution with 1 degree of freedom.

The number and percentage of subjects who experienced a seizure or censoring and the KM seizure free rate (and 2-sided 95% CI) by Day 182 were presented by treatment group for each stratum and overall. The stratified seizure freedom rate (and 2-sided 95% CI) at Day 182 for each treatment group and the difference between treatment groups were presented. The statistical evaluation of the noninferiority of LCM versus CBZ-CR was presented according to the 2 noninferiority criteria specified above. If the lower limit of $CI_{LCM\ CBZ}$ was >0, the p-value of the superiority test was to be shown. A KM survival plot was presented by treatment group for each stratum and overall.

The same methods as described for the primary efficacy variable were applied to other study populations for various sensitivity analyses.

The same methods described for the primary efficacy variable were repeated for the FAS and the PPS for the subgroups.

A Cox proportional hazard model was used to explore baseline variables that could be predictive of the time to first seizure during the 6-month seizure freedom evaluation period, after controlling for the stratification factor and treatment effect. The base model included treatment as a covariate and past 3-month seizure count (≤2 and >2) as strata. Additional covariates were added using a step-wise procedure (significant at 0.1 to enter and significant at 0.05 to stay). Any additional covariates included in the final model were considered as predictive. This exploratory analysis was performed for the FAS.

Analyses of other efficacy variables were performed for the FAS. The same methods described for the primary efficacy variable were applied for other efficacy variables, but the statistical evaluation of the noninferiority of LCM versus CBZ-CR was not performed.

Analyses of exploratory variables (CGIC, PGIC, and health care resource use) were performed

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for the FAS, unless otherwise specified.

Lacosamide and CBZ plasma concentration were summarized using the SS. Descriptive statistics of LCM and CBZ plasma concentrations were presented by visit and actual dose. The actual dose was defined as the most recent dose administrated prior to PK sampling. The following parameters were calculated for each of the sampling points: n, nLOQ (number of measurements above or equal to the lower limit of quantification [LOQ]), arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum value.

Safety analyses

All safety analyses were based on the SS unless otherwise specified.

The number and percentage of subjects who were on study medication for ≤28, >28 to 182, >182 to 364, >364 to 546, and >546 days during the Treatment Period were summarized by treatment group. Mean exposure and duration of exposure were summarized using descriptive statistics for the following analysis period: Dose-Finding, Last Evaluated, Maintenance, and Treatment Periods.

Subject-years of exposure during the Treatment Period was presented by treatment group. Subject-years of exposure was calculated as the sum of days of exposure in all subjects, divided by 365.25. Duration of exposure and subject-years of exposure by dose during the Treatment Period was also summarized by treatment group.

Treatment-emergent AEs were defined as AEs that started on or after the date of first dose of study medication and within 30 days following the date of final study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose. If the date of the last dose of study medication was unknown, any AEs occurring after the first dose of study medication were considered treatment emergent. Pretreatment AEs were AEs with start dates prior to the first dose of study medication.

Treatment-emergent AEs were assigned to Dose Finding, Last Evaluation, Maintenance, and End of Study Periods based on the AE onset dates. Adverse Events were tabulated by MedDRA SOC and PT. The number and percentage of subjects experiencing each event at least once were summarized. Numbers of individual AE occurrences were also presented in selected tables. All summaries were presented by treatment group. All summaries were sorted alphabetically by SOC and by frequency of events within SOCs, starting with the most frequent in the LCM treatment group.

The following summaries were presented for the AEs:

- Pretreatment AEs (summarized for all subjects screened)

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- An overview summary of TEAEs by treatment group and analysis period. It included the numbers and percentages of subjects with at least 1 TEAE, at least 1 serious TEAE, at least 1 TEAE leading to discontinuation, at least 1 drug-related TEAE, at least 1 severe TEAEs, and death. The same overview was also presented by the last evaluated dose level. An overview summary of TEAEs during the Treatment Period was presented by age (<65 or ≥65 years old at study entry). An overview summary of TEAEs during the first 14 days following the date of first dose was presented.

- Incidence of TEAEs by analysis period (Treatment, Dose Finding, Last Evaluation, Maintenance, and End of Study Periods). Incidence of TEAEs during the Treatment Period were presented by age (<65 or ≥65 years old at study entry). Incidence of TEAEs during the first 14 days following the date of first dose.

- Incidence of TEAEs occurring in at least 1% of subjects in any treatment group during the Treatment Period

- Subject number listing for TEAEs during the Treatment Period

- Incidence of TEAEs by dose at onset during the Treatment Period (Dose at AE onset was based on the randomized treatment group and protocol incorporating any scheduled dose changes. Dose at onset for an AE starting prior to the first dose or after the last dose of study medication was assigned to 'Not Applicable' and was not included in this summary). The same summary was presented by age (<65 or ≥65 at study entry). Incidence of serious TEAEs and TEAEs leading to discontinuation during the Treatment Period by dose at onset. If an AE start date was partial or completely missing, the dose at onset was derived based on the imputed AE start date.

- Incidence of TEAEs by maximum intensity during the Treatment Period (if the intensity of an AE was missing, it was assumed to be most severe)

- Incidence of TEAEs during the Treatment Period by maximum relationship per investigator (if the relationship was missing, the AE was assumed to be related to study medication.)

- Incidence of serious TEAEs by analysis period (Treatment, Dose-Finding, Last Evaluation, and Maintenance Periods). Incidence of serious TEAEs during the Treatment Period was presented by age (<65 or ≥65 years old at study entry). Incidence of serious TEAEs during the first 14 days following the date of first dose.

- Subject number listing for Serious TEAEs during the Treatment Period

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- Incidence of TEAEs leading to discontinuation by analysis period (Treatment, Dose-Finding, Last Evaluation, and Maintenance Period). Incidence of TEAEs leading to discontinuation during the Treatment Period by age (<65 or ≥65 years old at study entry). Incidence of TEAEs leading to discontinuation during the first 14 days following the date of first dose.

- Subject number listing for TEAEs leading to discontinuation during the Treatment Period

- Incidence of other significant TEAEs during the Treatment Period (Other significant AEs are defined by the MedDRA terms in Section 11.6). Incidence of other significant TEAEs during the first 14 days following the date of first dose was presented.

- Subject number listing for all deaths

- Incidence of TEAEs during the Treatment Period by age (<65 or ≥65 years old at study entry)

- Incidence of TEAEs during the Treatment Period by gender (male or female)

- Incidence of TEAEs during the Treatment Period by race (white or nonwhite)

- For continuous laboratory variables (hematology, clinical chemistry, urinalysis [continuous], thyroid and sex hormones, and lipids), summary statistics of actual values and change from Baseline were presented by visit and treatment group. In addition, summary statistics for the actual value and change from Baseline were presented for the last, minimum, and maximum post-Baseline values obtained during the Treatment Period. For categorical urinalysis parameters, the number and percentage of subjects identified as "negative," "trace," "1+," "2+," and "3+" were presented by visit and treatment group.

Shifts from Baseline to the maximum and minimum values during the Treatment Period based on the normal range (ie, low, normal, high, and missing) were presented for hematology, clinical chemistry, thyroid and sex hormones, and lipids.

A shift table that cross-tabulated Baseline versus maximum values during the Treatment Period in categories of <1x upper limit of normal (ULN), 1 to <2xULN, 2 to <3xULN, ≥3xULN, and missing was presented for liver function tests, which included alanine aminotransferase (ALT), aspartate aminotransferase, gamma glutamyl transferase (GGT), total bilirubin, and alkaline phosphatase.

The number and percentage of subjects with treatment-emergent marked laboratory abnormalities (hematology and clinical chemistry) were summarized by laboratory parameter, analysis period (Dose-Finding, Last Evaluation, Maintenance, and Treatment Periods), and treatment group. Treatment-emergent was defined as meeting the criteria at any post-Baseline

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visit during the Treatment Period and not meeting the same criteria during the Screening Period. In addition, the number and percentage of subjects with treatment-emergent marked abnormalities for the combination of total bilirubin ≥2xULN and ALT ≥3xULN were also presented.

Descriptive statistics were provided for the summary of laboratory assessments, vital signs, body weight, and ECGs. In addition, the number and percentage of subjects with a ≥10% change from Baseline in body weight at any visit (scheduled and unscheduled) during the Treatment Period were presented by treatment group.

Summary statistics of the actual values and change from Baseline for vital signs were presented by visit and treatment group. Actual values and change from Baseline were also presented for the last, minimum, and maximum post-Baseline values obtained during the Treatment Period. The number and percentage of subjects with abnormal vital signs were presented by visit and treatment group.

Summary and conclusions:

Subject disposition: A total of 530 subjects (59.8%) completed the study and 356 subjects (40.2%) discontinued from the study. Overall, the most common reasons for discontinuation were AEs (13.2%), consent withdrawn (9.5%), and LOE (8.8%). In the LCM and CBZ-CR treatment groups, 266 subjects (59.9%) and 264 subjects (59.7%), respectively, completed the study, and 178 subjects (40.1%) and 178 subjects (40.3%), respectively, discontinued from the study. The most common reasons for discontinuation were the same in both treatment groups: AE (10.8% and 15.6%), LOE (10.6% and 7.0%), and consent withdrawn (10.4% and 8.6%) in the LCM and CBZ-CR treatment groups, respectively.

A total of 119 subjects were in the ≥65 years of age group (62 subjects in the LCM treatment group and 57 subjects in the CBZ-CR treatment group). Among the subjects ≥65 years of age in the LCM and CBZ-CR treatment groups, 38 subjects (61.3%) and 29 subjects (50.9%), respectively, completed the study, and 24 subjects (38.7%) and 28 subjects (49.1%), respectively, discontinued from the study. The most common reason for discontinuation in subjects ≥65 years of age in the LCM treatment group was AEs (21.0%), followed by LOE and consent withdrawn (6.5% for each). The most common reason for discontinuation in subjects ≥65 years of age in the CBZ-CR treatment group was AE (26.3%) followed by LOE (8.8%), and protocol violation and consent withdrawn (7.0% for each).

Efficacy results: The primary efficacy variable was the proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject.

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- In the FAS, the stratified KM estimate of the proportion of subjects seizure free for 6 months at the last evaluated dose level was 89.8% (95% CI: 86.8%, 92.8%) in the LCM treatment group and 91.1% (95% CI: 88.2%, 94.0%) in the CBZ-CR treatment group. The difference in stratified seizure-freedom rate (and 2-sided 95% CI) between the LCM and CBZ-CR groups was -1.3% (-5.5%, 2.8%) with a relative ratio of -6.0% to the seizure freedom rate in the CBZ-CR treatment group. In the PPS, the stratified KM estimate of the proportion of subjects seizure free for 6 months at the last evaluated dose was 91.5% (95% CI: 88.6%, 94.3%) in the LCM treatment group and 92.8% (95% CI: 90.0%, 95.5%) in the CBZ-CR treatment group. The difference in stratified seizure freedom rate (and 2-sided 95% CI) between the LCM and CBZ-CR treatment groups at Day 182 (6 months) was -1.3% (-5.3%, 2.7%) with a relative ratio of -5.7%. The lower limit of the CI (-5.3%) was greater than the prespecified noninferiority confidence limit of -12%. Because LCM achieved both of the predefined noninferiority criteria (an absolute difference criterion of -12% and a relative difference criterion of -20%) in the FAS and the PPS, LCM can be considered as noninferior to CBZ-CR based on the proportion of subjects seizure free for 6 months at the last evaluated dose level.

- Noninferiority criteria were met for all sensitivity analyses and are consistent in supporting the primary analysis. The results of the sensitivity analyses indicate that the primary efficacy results were robust and interpretation of the primary analysis evaluation for 6-month seizure freedom was not affected by discontinuations, missing data, censoring, or exclusion of subjects due to important protocol deviations.

- Noninferiority of LCM to CBZ-CR based on the 6-month seizure-freedom rate was demonstrated in the diagnosed partial-onset or unclassified epilepsy subgroup and the diagnosed partial-onset epilepsy subgroup demonstrating that the 6-month seizure freedom results were robust and the interpretation was not impacted by inclusion of subjects with unclassified epilepsy or with unclassified epilepsy confirmed to be generalized epilepsy by the end of the study.

The results of the other efficacy variables are summarized below.

- In the FAS, the stratified KM estimate of the proportion of subjects seizure free for 12 months was 77.8% (95% CI: 73.4%, 82.2%) in the LCM treatment group and 82.7% (95% CI: 78.5%, 86.8%) in the CBZ-CR treatment group. The difference in stratified seizure-freedom rate (and 2-sided 95% CI) between the LCM and CBZ-CR at Day 364 was -4.9 (95% CI: -10.9%, 1.1%). Although no formal noninferiority evaluation was performed, the proportions of subjects in both the LCM and CBZ-CR treatment groups who

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remained seizure free for 12 consecutive months were similar.

- Some subjects in both treatment groups required escalation to higher dose levels to achieve 6-month seizure freedom and 12-month seizure freedom.

- In the elderly subgroup, the stratified KM estimate of the proportion of subjects who were seizure free for 6 months in the LCM and CBZ-CR treatment groups was similar (93.6% [95% CI: 87.8%, 99.5%] and 92.3% [95% CI: 83.9%, 100.0%], respectively). However, a higher proportion of elderly subjects in the LCM treatment group (72.6%) compared with the CBZ-CR treatment group (59.6%) completed the 6-month seizure freedom evaluation period and were seizure free at the last evaluated dose level. While the stratified KM estimate of the proportion of subjects seizure free for 6 months in the LCM and CBZ-CR treatment groups was similar, the higher proportion of subjects completing 6 months seizure free in the LCM treatment group compared with the CBZ-CR treatment group is due the higher rate of discontinuation observed in the CBZ-CR treatment group compared with the LCM treatment group in the elderly subgroup.

- Similar efficacy results between the LCM and CBZ-CR treatment groups were observed based on the other efficacy variables.

The results of the exploratory variables are summarized below.

- CGIC and PGIC results were comparable between the LCM and CBZ-CR treatment groups.

- Health care resource use was comparable between the LCM and CBZ-CR treatment groups.

Pharmacokinetics results: The LCM and CBZ-CR plasma concentration data separated by actual dose per intake reflect that subjects were treated with active drug and nearly all of the resulting concentrations are within the expected ranges for LCM and CBZ-CR.

Safety results: Treatment with LCM in this study was generally well tolerated in subjects newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or tonic-clonic seizures at doses up to 600mg/day when used as monotherapy for a mean duration of exposure of approximately 1 year when compared with CBZ-CR at doses up to 1200mg/day.

- The mean durations of LCM (328.6 days) and CBZ-CR (318.6 days) exposure during the Treatment Period were similar and consistent with the planned durations according to the study design. The total subject-years of exposure to LCM and CBZ-CR during the Treatment Period were 399.5 and 385.5 subject-years, respectively. The median of the mean exposure to LCM per subject was 198.18mg/day and the median of the mean exposure to CBZ-CR per

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subject was 396.36mg/day during the Treatment Period, consistent with the observation that most subjects remained at the first dose level.

- Overall, during the Treatment Period 328 subjects (73.9%) and 332 subjects (75.1%) in the LCM and CBZ-CR treatment groups, respectively, experienced at least 1 TEAE. In the LCM and CBZ-CR treatment groups, respectively, SAEs occurred in 32 subjects (7.2%) and 43 subjects (9.7%), AEs leading to permanent discontinuation occurred in 47 subjects (10.6%) and 69 subjects (15.6%), and drug-related TEAEs occurred in 165 subjects (37.2%) and 203 subjects (45.9%).

- The most common TEAEs during the Treatment Period (reported in at least 3% of subjects) in the LCM treatment group were headache (13.7%), dizziness (11.7%), fatigue (7.2%), nasopharyngitis (6.3%), and somnolence (5.4%). The most common TEAEs during the Treatment Period (reported in at least 3% of subjects) in the CBZ-CR treatment group were headache (12.9%), fatigue (10.4%), somnolence (9.3%), dizziness (8.6%), GGT increased (8.1%), nasopharyngitis (6.6%), nausea (5.0%), hypercholesterolemia (4.8%), constipation (4.3%), diarrhea (3.8%), urinary tract infection, ALT increased (3.4% for each), and rash (3.2%).

- Among the most commonly reported TEAEs (≥3%) during the Treatment Period, dizziness occurred with a higher incidence (≥2% difference) in the LCM compared with the CBZ-CR treatment group (11.7% vs 8.6%); GGT increased (8.1% vs 1.6%), somnolence (9.3% vs 5.4%), constipation (4.3% vs 0.7%), fatigue (10.4% vs 7.2%), and hypercholesterolemia (4.8% vs 2.5%) occurred with a higher incidence (≥2% difference) in the CBZ-CR treatment group compared with the LCM treatment group.

- In both the LCM and CBZ-CR treatment groups, TEAEs occurred at the highest incidence in the Dose-Finding and Last Evaluation Periods compared with the Maintenance and End of Study Periods. The incidence of TEAEs was >5% lower for the LCM treatment group compared with the CBZ-CR treatment group during the Dose-Finding (47.7% vs 54.8%, respectively) and Last Evaluation Periods (45.6% vs 52.1%, respectively); however, the incidences were similar between the 2 treatment groups for Maintenance and End of Study Periods.

- The incidence of TEAEs did not consistently increase with increasing dose level for subjects in the LCM treatment group. Among the small number of subjects receiving the highest doses (LCM up to 600mg/day and CBZ-CR up to 1200mg/day), the overall incidence of the most commonly reported TEAEs was not higher and no unexpected TEAEs were observed as

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compared with the lower doses.

- Most TEAEs were mild or moderate in both treatment groups. Thirty subjects (6.8%) and 42 subjects (9.5%) in the LCM and CBZ-CR treatment groups, respectively, reported TEAEs with a maximum intensity of severe. Severe TEAEs for the LCM and CBZ-CR treatment groups were most frequently reported in the system organ class (SOC) of Nervous system disorders (14 subjects [3.2%] and 10 subjects [2.3%], respectively).

- A lower percentage of subjects in the LCM treatment group reported TEAEs considered related to study medication per the investigator during the Treatment Period (165 subjects [37.2%]) compared with the CBZ-CR treatment group (203 subjects [45.9%]). The incidence of TEAEs considered related to study medication per the investigator for the LCM and CBZ-CR treatment groups were most frequently reported in the SOC of Nervous system disorders (84 subjects [18.9%] and 90 subjects [20.4%], respectively).

- During the Treatment Period 47 subjects (10.6%) in the LCM treatment group and 69 subjects (15.6%) in the CBZ-CR treatment group permanently discontinued the study due to TEAEs. The most common (≥1%) SOCs leading to discontinuation in the LCM treatment group were Nervous system disorders (3.8%), Skin and subcutaneous tissue disorders (1.8%), General disorders and administration site conditions (1.4%) and Psychiatric disorders (1.4%). In the CBZ-CR treatment group, the most common (≥1%) SOCs leading to discontinuation were Skin and subcutaneous tissue disorders (5.4 %), Nervous system disorders (3.8%), Investigations (2.7%), Immune system disorders (1.4%), General disorders and administration site conditions (1.1%), and Gastrointestinal disorders (1.1%). A notably higher percentage of subjects in the CBZ-CR treatment group permanently discontinued the study as a result of TEAEs in the Skin and subcutaneous tissue disorders, Investigations, and Immune system disorders SOCs compared with subjects in the LCM treatment group, and subjects in the CBZ-CR treatment group discontinued the study more frequently compared with subjects in the LCM treatment group as a result of preferred terms (PTs) related to hypersensitivity or allergic skin reactions and increased liver function test results.

- In the LCM treatment group, a total of 72.5% of subjects <65 years of age reported at least 1 TEAE during the Treatment Period compared with 82.3% of subjects ≥65 years of age. In subjects ≥65 years of age, the only events which occurred at a higher incidences (≥5% difference) compared with subjects <65 years of age were fall (9.7% vs 0.8%, respectively), diarrhea (6.5% vs 1.3%, respectively), and tremor (6.5% vs 0.3%, respectively). In the CBZ-CR treatment group, a total of 73.8% subjects <65 years of age reported at least 1 TEAE during the Treatment Period compared with 84.2% of subjects

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≥65 years of age. In subjects ≥65 years of age, the only event which occurred at a higher incidence (≥5% difference) compared with subjects <65 years of age was constipation (8.8% vs 3.6%, respectively).

- For subjects ≥65 years of age, similar or higher incidences in the TEAE overview categories (any TEAEs, serious TEAEs, discontinuations due to TEAEs, drug-related TEAEs, severe TEAEs, and deaths), were observed in CBZ-CR treatment group compared with the LCM treatment group. The largest differences (≥5% difference) were observed in the incidences of TEAEs considered related to study medication per the investigator (35.5% and 52.6% in LCM and CBZ-CR treatment groups, respectively), serious TEAEs (12.9% and 21.1% in LCM and CBZ-CR treatment groups, respectively), and TEAEs leading to discontinuation (21.0% and 26.3% in LCM and CBZ-CR treatment groups, respectively).

- Among the subjects ≥65 years of age, TEAEs occurring in ≥5% of subjects in either treatment group with a higher (≥5% difference) incidence in the LCM treatment group included fall (9.7% vs 1.8%, respectively) compared with the incidences in the CBZ-CR treatment group. For the CBZ-CR treatment group, headache (14.0% vs 6.5%, respectively), somnolence (12.3% vs 4.8%, respectively), GGT increased (10.5% vs 0%, respectively), constipation (8.8% vs 1.6%, respectively), and eosinophilia (5.3% vs 0%, respectively), were higher (≥5% difference) compared with the incidences in the LCM treatment group.

- No clinically relevant differences in the incidence of TEAEs by gender and by race for both the LCM and CBZ-CR treatment groups were observed

- Twenty-three cardiac-related TEAEs were reported by a total of 20 subjects in the LCM (12 events) and CBZ-CR (11 events) treatment groups during the Treatment Period, including sinus bradycardia (5 subjects [1.1%] and 6 subjects [1.4%], respectively), bradycardia (4 subjects [0.9%] and 3 subjects [0.7%], respectively), atrial fibrillation (1 subject [0.2%] in each treatment group), and heart rate decreased (1 subject [0.2%] in the LCM treatment group).

- Nine subjects reported 11 TEAEs related to suicidality during the Treatment Period, including suicidal ideation (4 subjects [0.9%] each in the LCM and CBZ-CR treatment groups) and depression suicidal, self-injurious behavior, and suicide attempt (1 subject [0.2%] each in the LCM treatment group).

- Seven subjects (1.6%) reported 7 TEAEs of syncope in the LCM treatment group and 1 subject (0.2%) reported syncope in the CBZ-CR treatment group during the Treatment Period. Only 1 of the events of syncope in the LCM treatment group was serious and led to

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discontinuation. The majority of subjects had predisposing factors for syncope
(ie, cardiovascular disease or history of syncope).

- The incidence of TEAEs of relevance to the partial-onset seizure population was low.

  − The most frequently reported seizure-related TEAE in the LCM treatment group was complex partial seizures (6 subjects [1.4%]); one of the events was serious and none of the events led to discontinuation. The most frequently reported seizure-related TEAE in the CBZ-CR treatment group was partial seizures with secondary generalization (5 subjects [1.1%]); three of these events were considered serious and 2 of the events led to discontinuation of study medication.

  − Nine subjects (2.0%) in the LCM treatment group reported memory impairment and 2 subjects (0.5%) each reported cognitive disorder and amnesia; none of the events were considered serious and none led to discontinuation. In the CBZ-CR treatment group, 5 subjects (1.1%) reported memory impairment, 3 subjects (0.7%) reported cognitive disorder, and 2 subjects (0.5%) reported amnesia; none of the events were considered serious and none led to discontinuation.

  − There were no TEAEs of psychotic disorder, epileptic psychosis, or acute psychosis reported during the study.

  − In the LCM treatment group, 8 subjects (1.8%) reported weight decreased and 3 subjects (0.7%) reported weight increased. In the CBZ-CR treatment group, 2 subjects (0.5%) reported weight decreased and 6 subjects (1.4%) reported weight increased. None of the events of body weight decreased or body weight increased in either treatment group were serious. In the CBZ-CR treatment group, 1 event of body weight increased led to study discontinuation. No other events of weight decreased or weight increased in either treatment group led to study discontinuation.

- Two subjects died during the study; 1 due to subarachnoid hemorrhage in the LCM treatment group and 1 due to ischemic stroke in the CBZ-CR treatment group. Both were considered to be not related to study medication per the investigator.

- Mean increases from Baseline of PR interval duration for the LCM treatment group (range: 4.8 to 12.8ms) and for the CBZ-CR treatment group (range: 4.6 to 10.8ms) were observed at most time points. Mean increases from Baseline of QRS interval (1 to 5ms) were observed at most post-Baseline time points in both the LCM and CBZ-CR treatment groups. At all post-Baseline time points, there was no evidence of QT, Bazett corrected QT, or Fridericia

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corrected QT prolongation following treatment with either LCM or CBZ-CR.

- The majority of subjects in both treatment groups had normal neurological examination results at Baseline and at each visit across all neurological parameters assessed (mental status, cranial nerves, reflexes, motor system, muscle strength, motor tone, and upper/lower extremities sensation).

- In general, there were no clinically relevant effects of LCM treatment observed for laboratory parameters, body weight, or vital signs. For the CBZ-CR treatment group, clinically relevant changes from Baseline in the laboratory values were related to hepatic enzymes (ALT and GGT) and thyroid hormones (thyroxine). Changes were also observed in sex hormones and lipids after CBZ-CR treatment but with less clinical significance.

Conclusions: This study compared the efficacy and safety of LCM (200 to 600mg/day) to CBZ-CR (400 to 1200mg/day) used as monotherapy for at least 1 year in subjects newly or recently diagnosed with epilepsy and experiencing partial-onset seizures or generalized tonic-clonic seizures. Noninferiority of LCM compared with CBZ-CR was demonstrated based on 6-month seizure freedom at the last evaluated dose level. Similar efficacy between LCM and CBZ-CR was observed in all other efficacy variables, including 12-month seizure freedom at the last evaluated dose level.

Lacosamide was safe and generally well tolerated at all dose levels (LCM 200 to 600mg/day), and no new safety concerns were identified for LCM. A favorable benefit-risk balance for LCM monotherapy was demonstrated in the studied population, including elderly subjects.

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